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## **Prevalence, Predictors and Prognosis of Depressive Disorders in the General Population**



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# **PREVALENCE, PREDICTORS AND PROGNOSIS OF DEPRESSIVE DISORDERS IN THE GENERAL POPULATION**

**A LONGITUDINAL POPULATION STUDY**

**Niina Markkula**

ACADEMIC DISSERTATION

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To my family

# ABSTRACT

Depressive disorders are a major public health concern worldwide due to their pervasiveness, often chronic or recurrent course and serious adverse outcomes. These include psychosocial disability, reduced quality of life, physical health problems and increased mortality. This study examined prevalence, predictors and different adverse outcomes of depressive disorders (major depressive disorder and dysthymia) in a general population setting. Specifically, the study aimed to establish the prevalence of depressive disorders in Finland in 2011 and assess possible changes over the past decade; to examine risk factors for new-onset depressive disorders; to investigate the long-term prognosis of depressive disorders and its determinants; and to assess excess mortality associated with depressive, anxiety and alcohol use disorders. A large longitudinal study of the Finnish population, consisting of the Health 2000 and Health 2011 Surveys, was used to investigate these questions. The survey data was complemented with data from the Care Register for Health Care and the Finnish Causes of Death Statistics.

The results show that one in 10 adults in Finland suffered from a depressive disorder in 2011, and the prevalence increased from 2000 to 2011, particularly among women. Methods to account for non-participation also showed that the non-participation of people with depressive disorders in population studies significantly biases prevalence estimates. People who were younger, had a history of multiple childhood adversities, lower trust axis of social capital, or an anxiety disorder or subclinical depressive symptoms at baseline, had a higher risk of developing depressive disorders. In addition, having three or more physical diseases was a risk factor for dysthymia. Among people with depressive disorders at baseline, 34-43% still had some depressive, anxiety or alcohol use disorder after 11 years, and 48-61% had clinically significant depressive symptoms. Unmarried people and those with more severe initial symptoms had a higher risk of persistent course. People with depressive disorders had a twofold mortality risk, whereas the risk was 1.7-fold in alcohol use disorders and was not increased in anxiety disorders, when adjusted for other risk factors.

This study confirms that depression is an increasing public health concern in Finland, and that depressive disorders have serious long-term consequences. To reduce the burden of depressive disorders, it is of key importance to develop primary prevention efforts and measures to reduce the negative health and social consequences of depression.

# TIIVISTELMÄ

Masennushäiriöt ovat merkittävä kansanterveydellinen ongelma maailmanlaajuisesti. Ne ovat yleisiä, usein pitkäkestoisia ja niillä on suuri taipumus uusiutua. Niihin liittyy vakavia kielteisiä seurauksia, kuten psykososiaalista haittaa, heikentynyttä elämänlaatua, fyysisen terveyden ongelmia ja lisääntynyttä kuolleisuutta. Tässä tutkimuksessa selvitettiin masennushäiriöiden (masennustilan sekä pitkäkestoisen masennuksen) esiintyvyyttä, riskitekijöitä ja erilaisia kielteisiä seurauksia pitkittäisessä väestötutkimuksessa. Tutkimuksen tavoitteina oli selvittää masennushäiriöiden esiintyvyys Suomessa vuonna 2011 ja arvioida esiintyvyyden mahdollisia muutoksia viime vuosikymmenen aikana, tutkia masennushäiriöiden ilmaantuvuuden riskitekijöitä, selvittää masennushäiriöiden pitkän aikavälin ennustetta ja siihen vaikuttavia tekijöitä sekä arvioida masennus-, ahdistus- ja alkoholihäiriöihin liittyvää ylikuolleisuutta. Tutkimusaineistona käytettiin Terveys 2000 - ja Terveys 2011 -tutkimuksia, jotka muodostavat yhdessä pitkittäisen väestötutkimuksen. Väestötutkimuksen tietoja täydennettiin hoitoilmoitusrekisterin ja kuolemansyyrekisterin tiedoilla.

Tulokset osoittavat, että yhdellä kymmenestä suomalaisesta aikuisesta oli masennushäiriö vuonna 2011. Masennushäiriöiden esiintyvyys lisääntyi vuosien 2000 ja 2011 välillä erityisesti naisilla. Väestötutkimusten perusteella tehdyt arviot masennushäiriöiden esiintyvyydestä voivat olla todellista pienempiä, koska niistä kärsivät henkilöt osallistuvat väestötutkimuksiin muita harvemmin. Riskitekijöitä uusien masennushäiriöiden ilmaantumiselle olivat nuori ikä, useat lapsuuden vastoinkäymiset, ahdistuneisuushäiriö, lievät masennuksen oireet jo tutkimuksen alussa sekä sosiaalisen pääoman ulottuvuuksista heikko kyky tuntea luottamusta. Niistä seurantatutkimuksen henkilöistä, joilla oli tutkimuksen alussa masennushäiriö, 34-43 %:lla oli todettavissa masennus-, ahdistus- tai alkoholihäiriö yhdentoista vuoden kuluttua seurantatutkimuksessa, ja 48-61 %:lla oli kliinisesti merkittäviä masennusoireita. Riski häiriön pitkittymiselle oli suurempi niillä, joilla oli muita vaikeampia oireita vuonna 2000, sekä niillä, jotka eivät olleet naimisissa tai avoliitossa. Masennushäiriöihin liittyi kaksinkertainen kuolleisuusriski, alkoholihäiriöissä riski oli 1,7-kertainen, kun taas ahdistushäiriöissä riski ei ollut suurentunut.

Tämä tutkimus vahvistaa, että masennushäiriöt ovat kasvava kansanterveysongelma Suomessa ja niillä on vakavia pitkäaikaisia seurauksia. On erittäin tärkeää kehittää sekä ennaltaehkäisyä että

toimenpiteitä, joilla vähennetään masennushäiriöiden kielteisiä terveydellisiä ja sosiaalisia seurauksia.

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Niina Markkula

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# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I            Markkula N, Suvisaari J, Saarni SI, Pirkola S, Peña S, Saarni SE, Ahola K, Mattila AK, Viertiö S, Strehle J, Koskinen S, Härkänen T. *Prevalence and correlates of major depressive disorder and dysthymia in an eleven-year follow-up - results from the Finnish Health 2011 Survey* Journal of Affective Disorders 2015 (173) 73-80
- II           Markkula N, Marola N, Nieminen T, Koskinen S, Saarni SI, Härkänen T, Suvisaari J. *Predictors of new-onset depressive disorders in the working-age population – results from the longitudinal Finnish Health 2011 Study*. Submitted for publication
- III          Markkula N, Härkänen T, Nieminen T, Peña S, Mattila AK, Koskinen S, Saarni SI, Suvisaari J. *Prognosis of depressive disorders in the general population– results from the longitudinal Finnish Health 2011 Study*. Journal of Affective Disorders 190 (2016) 687–696
- IV          Markkula N, Härkänen T, Perälä J, Partti K, Peña S, Koskinen S, Lönnqvist J, Suvisaari J, Saarni SI., *Mortality in people with depressive, anxiety and alcohol use disorders in Finland*. Br J Psychiatry, 2012. 200(2): p. 143-9.

The publications are referred to in the text by their Roman numerals.



## ABBREVIATIONS

AUD	Alcohol use disorder
BDI	Beck Depression Inventory
BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies Depression Scale
CIDI	Composite International Diagnostic Interview
CIS-R	Clinical Interview Schedule (Revised)
DALY	Disability Adjusted Life-Year
DEPS	Depression Scale
DIS	Diagnostic Interview Schedule
DPAX	Depression and Anxiety Schedule
DSM	Diagnostic and Statistical Manual
GAD	Generalised anxiety disorder
GBD	Global Burden of Disease
GHQ	General Health Questionnaire
HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamus-pituitary-adrenal (axis)
HSCL	Hopkins Symptom Checklist
ICD-10	International Classification of Diseases, 10th revision
ICPE	International Consortium in Psychiatric Epidemiology
IPW	Inverse probability weights
ISPI	Iowa Structured Psychiatric Interview
M-CIDI	Composite International Diagnostic Interview, Munich version
MDD	Major depressive disorder
MDE	Major depressive episode
MI	Multiple imputation
MINI	Mini-International Neuropsychiatric Interview
NCS-R	National Comorbidity Survey, Replication
OR	Odds ratio
PDD	Persistent depressive disorder
PERI	Psychiatric Epidemiological Research Instrument
PHQ-G	Personal Health Questionnaire
PHQ	Patient Health Questionnaire
PSE	Present State Examination
WHO	World Health Organization
WMHS	World Mental Health Survey
SADS	Schedule for Affective Disorders and Schizophrenia
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM
SCL-90	Symptom Checklist 90 items
SSRI	Selective serotonin reuptake inhibitors
YLD	Years lived with disability

YLL	Years of life lost
etc.	et cetera
i.e.	id est
e.g.	exempli gratia

# 1 INTRODUCTION

Depression can be used to describe everyday feelings of sadness. However, it also refers to a psychiatric disorder whose key feature is a sad or depressed mood, accompanied by other distinct symptoms, including loss of interest, fatigue, memory problems, insomnia and recurrent thoughts of death. Typically, the disorder causes suffering and renders the person affected partly or fully unable to carry on with everyday life.

Every year, approximately one in 20 people suffers from major depressive disorder (MDD) (Ferrari *et al.*, 2013c). However, this rough estimate depends on how the exact criteria of the disorder are defined, how it is measured, and in which population, country and continent the study is carried out (Kessler and Bromet, 2013). The annual prevalence of dysthymia (another common depressive disorder with typically a more chronic course than MDD) is much lower, estimated at 1-2% (Charlson *et al.*, 2013, Gureje, 2011, Waraich *et al.*, 2004). From 9-16% of the population may have a depressive disorder severe enough to warrant specialised medical care over the course of their lifetime (Pedersen *et al.*, 2014) and many more will suffer from a less severe form. Increased awareness of depression in society and increased use of antidepressants has led many to believe that the prevalence of depression has increased, but there have been no indications of this in previous population studies (Ferrari *et al.*, 2013c, Patten *et al.*, 2015a).

Depression is more common among women, younger people, unmarried or divorced individuals, and those in a socially disadvantaged position (Kessler and Bromet, 2013). It is not clear, however, whether the association between these factors and depression necessarily implies causation. Some factors may increase the risk of developing depression, while others decrease the likelihood of recovery.

The age of onset of depression is typically in the early 20s, but there is wide variation (Kessler and Bromet, 2013). On average, an illness episode lasts a few months (Eaton *et al.*, 2008b, Kessler *et al.*, 2003, Spijker *et al.*, 2002), but a chronic or recurrent course is regrettably common (Eaton *et al.*, 2008b, Spijker *et al.*, 2002). Depression may negatively impact educational attainment, marital relations, employment, parental functioning, as well as general health status and mortality risk (Kessler and Bromet, 2013). The risk of suicide increases as much as 20-fold compared to people without depression, and 4-7% of depressed individuals die by suicide (Holmstrand *et al.*, 2015, Isometsä, 2014, Nordentoft *et al.*, 2011).

The aim of this study is to examine prevalence, predictors and different adverse outcomes of depressive disorders in a general population setting. The study is based on two large health examination surveys of the Finnish population, the Health 2000 study and its follow-up study, the Health 2011 Survey. In addition, register data on hospitalisations and mortality is utilised.

## **2 REVIEW OF THE LITERATURE**

### **2.1 DEFINITION OF DEPRESSIVE DISORDERS**

Depressive disorders refer to conditions that are characterised by sad or depressed mood and also entail other symptoms, such as inability to experience pleasure, feelings of guilt, thoughts of death, cognitive symptoms (such as diminished ability to think or concentrate) and physical changes (such as insomnia and loss of appetite). These disorders cause emotional and physical suffering, and often lead to reduction in functional capacity and the ability to work.

The pathophysiology, or mechanism of how depressive disorders develop in the human body, is not clear. This is why the diagnostic criteria rely on describing a collection of symptoms considered essential and characteristic of the disorder. Currently, two diagnostic systems are in place: the International Classification of Diseases, 10<sup>th</sup> revision (ICD-10), and the Diagnostic and Statistical Manual, fourth and fifth revisions (DSM-IV and DSM-5). The ICD-10 is used by health care systems in many countries, including Finland, whereas the DSM-IV and DSM-5 are frequently used in research. Both criteria are presented here.

#### **2.1.1 ICD-10**

According to the ICD-10 Classification of Mental and Behavioural Disorders (WHO, 1993), a depressive episode (code F32) is a condition that lasts a minimum of two weeks and is characterised by at least two of three core symptoms: depressed mood that is present for most of the day and almost every day; loss of interest in activities that the person normally enjoys; and fatigue or decreased energy. In addition, one or more of the following symptoms must also be present, so that there are a minimum of four: loss of confidence and self-esteem; excessive and inappropriate guilt; recurrent thoughts of death, suicide or suicidal behaviour; diminished ability to think or concentrate; agitation or retardation; sleep disturbance; change in appetite and weight change. In addition to these symptom criteria, hypomanic or manic episodes should be excluded, as well as the symptoms attributable to psychoactive substance use or organic mental disorder.

Depressive episodes are further classified into mild (4-5 symptoms), moderate (6-7 symptoms) or severe (8-9 symptoms). If the person has had prior depressive episodes and recovered for a minimum of 2 months between episodes, the disorder is called “Recurrent depressive disorder” (F33).

Dysthymia (F34.1) is a condition of depressed mood either constantly or recurrently for a minimum of two years, in which periods of normal mood do not last for longer than a few weeks. Few or none of the episodes are severe enough to meet criteria for recurrent mild depressive disorder. Three of the following symptoms should be present during some of the periods of depression: reduction in energy or activity; insomnia; loss of self-confidence; difficulty concentrating; tearfulness; loss of interest in sex and other pleasurable activities; feelings of hopelessness; perceived inability to cope with everyday responsibilities; pessimistic attitude toward the future or brooding over the past; withdrawal from social activities; and being less talkative than normal. The onset of dysthymia may be early (adolescence to late 20s) or late, often following a depressive episode.

The ICD-10 also presents criteria for “Recurrent brief depressive disorder” (F38.10), in which recurrent episodes of equal intensity but shorter duration than depressive episode occur.

### **2.1.2 DSM-IV**

The DSM-IV criteria for major depressive disorder (MDD) (code 296.xx) include minimum duration of two weeks, presence of either depressed mood or anhedonia most of the day and nearly every day, and other symptoms of the following, for a minimum of five: significant change in appetite or weight; insomnia or hypersomnia; psychomotor retardation or agitation observable to others; fatigue or loss of energy; excessive or inappropriate guilt or worthlessness; diminished ability to think or concentrate; and recurrent thoughts of death or suicide. The disorder is classified into mild, moderate, severe or with psychotic features.

In addition to symptom and duration criteria, DSM-IV criteria require that the condition cause clinically significant distress or impairment in social, occupational or other areas. Exclusion criteria of mania, hypomania, substance use and somatic conditions are similar to ICD-10. In addition, the DSM-IV does not establish a diagnosis of MDD if symptoms are related to the loss of a loved one within the past two months, unless the symptoms include psychomotor retardation, excessive or inappropriate guilt, suicidality, psychotic symptoms, or are associated with a marked decrease in functional capacity.

Dysthymia (300.4) is described as a disorder where the mood is depressed for most of the day more than half of the time for two years or more, and two or more of the following symptoms are present: change in appetite; insomnia or sleeping too much; low energy; low self-esteem, poor concentration; and hopelessness. The symptoms should cause significant impairment in social,

work or other important areas. Symptom-free periods must be no longer than two months.

### 2.1.3 DSM-5

There were no changes to core symptoms or duration criteria for MDD between DSM-IV and DSM-5. A new specifier “with mixed features” was introduced to describe a depressive episode with a maximum of three manic symptoms. The most notable change was the omission of the bereavement exclusion. This was due to the fact that the time limit was considered arbitrary and not in line with actual duration of grieving, and because bereavement-related MDD does not differ from non-bereavement-related MDD in terms of risk factors, previous history of depression, and course or response to treatment (Kendler *et al.*, 2008, Uher *et al.*, 2014). In the DSM-5, bereavement is likened to other stressors that commonly influence the onset and course of MDD. In one study of individuals who experienced a brief major depressive episode (less than two months), 38% reported the disorder to be bereavement-related (McCabe and Christopher, 2015), with certain distinct differences to the non-bereavement related episodes, such as less suicidality and worthlessness.

In the DSM-5, dysthymia was reconceptualised as “persistent depressive disorder” (PDD) (300.4). This category includes both chronic major depressive disorder and former dysthymia. The change was made because no significant differences between these two conditions had been established, whereas significant differences appear to exist between chronic and non-chronic depression. Some 29% of individuals with lifetime depression are estimated to suffer from persistent depressive disorder (Murphy and Byrne, 2012).

“Premenstrual dysphoric disorder” (625.4) was moved from an appendix to the main category of depressive disorders. “Disruptive mood dysregulation disorder” (269.99) for children up to 18 years was also added to the category.

The changes to the diagnostic categories of depressive disorders in the DSM-5 may result in changes in prevalence (Uher *et al.*, 2014). Guidance on whether PDD and MDD can be diagnosed at the same time is contradictory, but according to PDD criteria: “If the symptom criteria are sufficient for a diagnosis of a major depressive episode at any time during this period, then the diagnosis of major depression should be noted, but it is coded not as a separate diagnosis but rather as a specifier with the diagnosis of persistent depressive disorder.” Therefore, it is possible that the prevalence of MDD will decrease, as chronic cases will be diagnosed as PDD. On the other hand, the omission of the bereavement exclusion may result in an increase in the

prevalence of MDD, given the large proportion of people who attributed a depressive episode to bereavement (McCabe and Christopher, 2015).

#### 2.1.4 MAIN DIFFERENCES BETWEEN THE DIAGNOSTIC SYSTEMS

The main differences in diagnostic criteria for MDD between the ICD-10 and the DSM (IV and 5) systems are: 1) the different number of symptoms required (four in ICD-10 and five in DSM); 2) different number of core symptoms (three in ICD-10 and two in DSM); and 3) the DSM criterion of “significant distress or functional impairment,” which the ICD-10 does not consider (Table 1).

In the case of dysthymia, the differences are: 1) minimum number of symptoms (four in ICD-10 and three in DSM); and 2) number of symptoms listed (12 in ICD-10 and seven in DSM).

**Table 1.** *Main differences in the diagnostic systems of depressive disorders: ICD-10, DSM-IV and DSM-5*

	Core symptoms	Number of symptoms (total)	Other criteria	Exclusion
<b>Major depressive disorder</b>				
ICD-10	Minimum 2 of the following: depressed mood, anhedonia, and decreased energy or fatigue	4	-	Hypomania, mania, symptoms attributable to psychoactive substance use or organic mental disorder
DSM-IV	Either depressed mood or anhedonia	5	Must cause clinically significant distress or impairment	Same as in ICD-10, and also if symptoms occur within 2 months of bereavement
DSM-5	As in DSM-IV	5	As in DSM-IV	Same as in ICD-10, no bereavement exclusion
<b>Dysthymia</b>				
ICD-10	Depressed mood either constantly or recurrently for a minimum of two years	4 (not necessarily at the same time)		Mania
DSM-IV	Depressed mood	3 from a list of 7		MDD in the first two years, mania, substance induced



## 2.2 PREVALENCE OF DEPRESSIVE DISORDERS

### 2.2.1 MEASUREMENT OF DEPRESSIVE DISORDERS IN POPULATION STUDIES

There is wide variation in prevalence of depressive disorders across countries. This is assumed to be due to real, existing variations and to methodological differences in the studies.

One issue is the diverse definitions of depression. Some studies include MDD only, whereas others measure MDE, including bipolar depression. Still others include dysthymia or depression not otherwise specified. Wider inclusion of diagnostic categories increases observed prevalence rates (Ferrari *et al.*, 2013c).

Diagnostic instruments also matter. When symptom scales are used as a basis of diagnosis, measured prevalences tend to be higher than when structured diagnostic interviews are used (Ferrari *et al.*, 2013c). Some studies have also found higher prevalences using ICD-10 instead of DSM-IV; in others no significant differences existed (Andrews *et al.*, 2001, Ferrari *et al.*, 2013c). Differences among studies in target population, sampling and participation rates also contribute to inaccuracies in prevalence estimates.

Finally, conceptual models of depression as well as the presentation of symptoms differ across cultures (Karasz, 2005, Ventevogel *et al.*, 2013). This limits the applicability of psychometric instruments designed for different cultural contexts. To enable comparison and for practical reasons, however, the same standardised and validated instruments are normally used in epidemiological studies, irrespective of the context.

#### 2.2.1.1 *Methods of assessing depressive disorders in population studies*

Population studies on psychiatric disorders require tools that are reliable, replicable and valid to the construct they are measuring, as well as feasibly applicable to thousands of persons at a reasonable cost. The latter requisite generally limits the time available and the type of professional who can administer the tool.

Two methods that meet these requirements are structured interviews and symptom scales. Structured interviews (or schedules) are designed to assess the presence of a psychiatric disorder dichotomously – the disorder either is or is not present. They were developed to enable psychiatric assessment in

population surveys using lay interviewer-administered tools (Brugha *et al.*, 1999). There are two types of structured interviews: semi-structured and fully structured interviews. A semi-structured interview is performed by a mental health professional, usually a psychiatrist or psychologist, and resembles a clinical examination, where the questions have a standard wording, but probing and further questions are flexible. In a fully structured interview, a trained lay interviewer asks the questions and clarifying questions or further details exactly as has been written, and codes answers according to instructions. The usefulness of a fully structured interview depends greatly on the exact wording and how understandable it is to the participants. In practice, due to human resource costs, population surveys always use fully structured interviews.

The most frequently used structured interview is the Composite International Diagnostic Interview (CIDI) in its various forms (see Chapter 4.2 for a more detailed description of this instrument). The most relevant structured interviews are listed in Table 2.

**Table 2.**      *Structured diagnostic interviews to assess depressive disorders in epidemiological studies, ordered by decade of first publication of the instrument*

<b>Structured diagnostic interviews (schedules) used to establish diagnosis of depression in epidemiological studies</b>			<b>Fully / Semi- structured</b>
PSE	Present State Examination	1960s	Semi
CIS (-R)	Clinical Interview Schedule (Revised)	1970s	Fully
SADS	Schedule for Affective Disorders and Schizophrenia	1970s	Semi
DIS	Diagnostic Interview Schedule	1980s	Fully
DPAX	Depression and Anxiety Schedule	1980s	Fully
ISPI	Iowa Structured Psychiatric Interview	1980s	Fully
MINI	Mini-International Neuropsychiatric Interview	1990s	Fully
SCAN	Schedules for Clinical Assessment in Neuropsychiatry (development of PSE)	1990s	Semi
CIDI	Composite International Diagnostic Interview (UM-CIDI, WMH-CIDI, M-CIDI) (development of DIS)	1990s	Fully
PRIME-MD	Primary Care Evaluation of Mental Disorders	1990s	Semi
SCID	Structured Clinical Interview for DSM (III-R, IV and 5) (development of SADS)	1990s	Semi

Symptom scales are designed to measure symptoms of a disorder in a dimensional scale. Sometimes these scales are used to identify people with possible depressive disorder by establishing a cut-off point, above which the

disorder is possible or probable. They are also used in clinical practice to monitor levels of symptoms, which is their original intended use. The most relevant self-reported depressive symptom scales are listed in Table 3.

**Table 3.** *Symptom scales to assess depressive symptoms, ordered by decade of first publication of the instrument*

**Symptom scales used to assess level of symptoms and establish possible diagnosis of depression**

HSCL	Hopkins Symptom Checklist	1950s
BDI	Beck Depression Inventory	1960s
Zung	Zung Depression Scale	1960s
CES-D	The Center for Epidemiologic Studies Depression Scale	1970s
HADS	Hospital Anxiety and Depression Scale	1980s
PERI	Psychiatric Epidemiological Research Instrument	1980s
BDI-II	Beck Depression Inventory II	1990s
SCL-90	Symptom Checklist 90 items (development of HSCL)	1990s
DEPS	The Depression Scale	1990s
PHQ-G	Personal Health Questionnaire	1990s
PHQ	Patient Health Questionnaire	2000s

The advantage of symptom scales over structured interviews is the shorter time needed, and the fact that they are self-administered. However, their diagnostic validity is limited (Pettersson *et al.*, 2015). In this literature review, studies using valid diagnostic procedures based on structured interviews are prioritised.

## **2.2.1.2 Methodological challenges in prevalence studies**

### **2.2.1.2.1 Non-participation of people with mental disorders**

When prevalence of mental disorders is assessed through population surveys, participation in these surveys may influence estimates of prevalence. Many studies indicate that people with psychiatric disorders have a lower likelihood of participating in population studies (Eaton *et al.*, 1992, Suvisaari *et al.*, 2009). Different types of psychiatric disorders have been found to contribute to non-participation (Haapea *et al.*, 2008). Disorder severity, however, may increase risk of non-participation in both psychotic and non-psychotic disorders (Haapea *et al.*, 2007, Lamers *et al.*, 2012). Conversely, studies in the Netherlands have found that non-participation was associated with correlates of mental disorders, such as low education, younger age and unemployment, but not the disorders themselves (de Graaf *et al.*, 2000, de Graaf *et al.*, 2013). These results have not been replicated in other studies.

Therefore, non-participation of people with psychiatric disorders may bias prevalence estimates. It is thus likely that true prevalences are higher than those estimated based on population surveys that do not correct for non-participation (Haapea *et al.*, 2008).

#### **2.2.1.2.2 Lifetime prevalence estimates**

Doubts on the accuracy of lifetime prevalence estimates in population surveys have been raised for two main reasons: the high ratio of period and lifetime prevalence rates; and the curvilinear association of lifetime prevalence estimates with age (Parker, 1987). In the first case, a low ratio of period to lifetime prevalence would be expected in the case of episodic disorders, such as depression. However, period prevalences of 50-60% of lifetime prevalence are often observed (Moffitt *et al.*, 2010, Parker, 1987). In the second case, one would assume an increasing prevalence of lifetime disorders with age. However, the lifetime prevalence of depression peaks at mid-life and then decreases.

Both observations are explained by recall bias, which is the systematic inaccuracy of reporting events that occurred in the past. The influence of recall bias on assessments of lifetime prevalence of mental disorders has been ascertained in several studies (Kruijshaar *et al.*, 2005, Moffitt *et al.*, 2010, Patten *et al.*, 2012, Takayanagi *et al.*, 2014). When comparing prospective to retrospective study settings, the rate of lifetime mental disorders was double in the prospective compared to retrospective assessment (Moffitt *et al.*, 2010). In the case of MDD, the increase is almost threefold: the lifetime prevalence evaluated retrospectively was 4.5%, whereas cumulative evaluation from several waves of a prospective survey yielded a lifetime prevalence of 13.1% (Takayanagi *et al.*, 2014). In another prospective study, only 40% of persons reported a past depressive episode, verified in a previous wave of the study, 10 years after it had occurred (Patten *et al.*, 2012). Finally, when the association of declining lifetime prevalence with age was examined, it was explained by recall bias, and possibly differential mortality rates, rather than cohort effect (Patten, 2003).

For these reasons, this literature review focuses on period prevalence only, and 12-month prevalence is presented whenever available.

### **2.2.2 GLOBAL PREVALENCE OF MAJOR DEPRESSIVE DISORDER**

The prevalence of major depressive disorder (MDD) varies widely depending on the population studied and the diagnostic instrument and diagnostic criteria used. A recent systematic review found the lowest prevalence (0.05%) in Japanese males aged 65 and older in 1998, using a structured

clinical interview (SCID). This review found the highest prevalence (73%) among women aged 15 and older in post-war Afghanistan in 2005, using a symptom scale (HSCL-25) (Ferrari *et al.*, 2013c).

When comparing representative adult population studies, differences still exist between studies, countries and regions. These variations are not explained by country income categories: applying standardised methodology across 18 countries, the WHO World Mental Health Surveys, (WMHS) found an average 12-month prevalence of 5.5% in high-income countries and 5.9% in low-income countries (Bromet *et al.*, 2011). In contrast, regional differences do exist, so that low prevalences are found in East and Southeast Asia and Sub-Saharan Africa, whereas higher prevalences are found in North and South America, North Africa and some European countries (Bromet *et al.*, 2011, Ferrari *et al.*, 2013c, Steel *et al.*, 2014).

Some variations are related to the methodological issues discussed in Chapter 2.1.1. But it is likely true that differences between countries do also exist. The WMHS used the same structured interview and similar sampling procedures in all participating countries, and still found fivefold differences in 12-month prevalence of MDE, varying from 2.2% in Japan to 10.4% in Brazil (Bromet *et al.*, 2011). Previously, it was thought that the differences might be due to different reporting thresholds. But analyses of the WMHS data demonstrate increasing disability with increasing prevalence, pointing at a true difference in prevalence rather than differences in interpretation or measurement (Kessler and Bromet, 2013).

Recent high-quality reviews of epidemiological literature of MDD have established a global point-prevalence (current or past month) of 4.7% and a “pooled period prevalence of mood disorder” (point or 12-month) of 5.4% (Ferrari *et al.*, 2013c, Steel *et al.*, 2014). Earlier systematic reviews and meta-analyses have placed the average 12-month prevalence in the range of 4.1% to 6.9% (Eaton *et al.*, 2008a, Waraich *et al.*, 2004, Wittchen *et al.*, 2011). Several nationally representative studies have found annual prevalences of 3.9% to 6.8% (Table 4). It can therefore be concluded that the global 12-month prevalence of MDD is approximately 5%, but that significant variations exist between countries and regions.

**Table 4.**      *Prevalence of depressive disorders in different general population studies*

Publication	Study setting	Instrument used	12-month prevalence of MDD
Bijl et al., 1998. Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl <i>et al.</i> , 1998)	Netherlands Mental Health Survey and Incidence Study- (NEMESIS), representative of the Dutch general population aged 18-64	CIDI	5.8%
Murphy et al., 2000. A 40-year Perspective on the Prevalence of Depression (Murphy <i>et al.</i> , 2000)	Stirling County Study, longitudinal general population study in Canada (general population aged 18 and older; in 1952 heads of households only)	DPAX 1 and 2, DIS	5.3% in 1952 and 1970, 2.9-5.7% in 1990 depending on instrument
Andrews et al., 2001. Prevalence, comorbidity, disability and service utilisation. (Andrews <i>et al.</i> , 2001)	Australian National Mental Health Survey, representative population study of persons 18 years and older	CIDI 2.1	6.7% (ICD-10), 6.3% (DSM-IV)
Kessler et al., 2003. The Epidemiology of Major Depressive Disorder. (Kessler <i>et al.</i> , 2003)	National Comorbidity Survey Replication (NCS-R), representative population survey of household residents aged 18 and older in the US	WHO-CIDI	6.6%
Hasin et al. 2005. Epidemiology of Major Depressive Disorder (Hasin <i>et al.</i> , 2005)	National Epidemiologic Survey on Alcoholism and Related Conditions, nationally representative population survey of household residents aged 18 and older in the US	Alcohol Use Disorder and Associated Disabilities Interview Schedule– DSM-IV Version (AUDADIS-IV)	5.3%
de Graaf et al., 2012. Prevalence of mental disorders and trends from 1996 to 2009. Results from the Netherlands Mental Health Survey and Incidence Study-2 (de Graaf <i>et al.</i> , 2012)	Netherlands Mental Health Survey and Incidence Study 2 (NEMESIS-2), representative of the Dutch general population aged 18-64	CIDI 3.0	5.2%
Patten et al. 2015 Descriptive Epidemiology of Major Depressive Disorder in Canada in 2012 (Patten <i>et al.</i> , 2015b)	Canadian Community Health Study—Mental Health (CCHS-MH), nationally representative study of persons 15 years and over	WHO-CIDI	3.9%
Jacobi et al., 2015. Twelve-months prevalence of mental disorders in the German Health Interview and Examination Survey for Adults – Mental Health Module (DEGS1-MH)	German Health Interview and Examination Survey for Adults Mental Health Module (DEGS1-MH), nationally representative study of	DEGS-CIDI	6.8%

(Jacobi <i>et al.</i> , 2015)	the population aged 18-79		
<b>Reviews and cross-national studies</b>			
Andrade <i>et al.</i> , 2003. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. (Andrade <i>et al.</i> , 2003)	Cross-national study of general populations with 10 low- to high-income countries included	WHO-CIDI, University of Michigan-CIDI and Munich-CIDI	Variation from 1.2% in Japan to 10.0% in the US (MDE, not MDD)
Waraich <i>et al.</i> , 2004. Prevalence and Incidence Studies of Mood Disorders: A Systematic Review of the Literature. (Waraich <i>et al.</i> , 2004)	Systematic review of general population studies	15 studies using standardised or clinical diagnostic tools were included	Pooled prevalence 4.1%
Wittchen and Jacobi, 2005. Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies. (Wittchen and Jacobi, 2005)	Review of 27 studies in 16 European countries	Varying, eg. CIDI, GHQ	Median prevalence 6.9%, variance 3.1-10.1% (MDE)
Wittchen <i>et al.</i> , 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. (Wittchen <i>et al.</i> , 2011)	Systematic literature reviews, re-analyses of existing data sets, national surveys and expert consultations	25 community studies on depression were included	5.7% from studies; 6.9% when taking into account expert estimates
Bromet <i>et al.</i> 2011. Cross-national epidemiology of DSM-IV major depressive episode (Bromet <i>et al.</i> , 2011)	World Mental Health Surveys, 18 countries with nationally representative adult samples	WHO-CIDI	Average prevalence 5.5% in high-income and 5.9% in low-income countries, variation from 2.2% to 10.4%
Ferrari <i>et al.</i> , 2013. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature (Ferrari <i>et al.</i> , 2013c)	Systematic review and meta-analysis of community prevalence studies	116 studies of prevalence with varying methodology, including structured interviews and symptom scales	4.7% (point prevalence)
Steel <i>et al.</i> , 2014. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013 (Steel <i>et al.</i> , 2014)	Random-effects meta-analysis of prevalence studies of all mental disorders, structured diagnostic interview methodology	174 studies from 63 countries published 1980-2013	Pooled period prevalence of mood disorder 5.4%

### 2.2.3 PREVALENCE OF DEPRESSIVE DISORDERS IN FINLAND

In Finland, there is a long tradition of extensive population health surveys that include instruments to measure depression. In 1978-1980, the Mini-Finland health survey included the Present State Examination (PSE) to assess prevalence of mental disorders. Some 8000 individuals from the general population, aged 30 years and over, were sampled. The prevalence of “neurotic depression” was 4.6% (Lehtinen *et al.*, 1990).

In 1996, the short form of the University of Michigan CIDI (UM-CIDI) was used to assess depression in a random sample of adults (15-75 years, n=5993). The 12-month prevalence of major depressive episode was 9.3% (Lindeman *et al.*, 2000). The short form of the UM-CIDI instrument, however, does not apply exclusions for organic or somatic conditions, nor does it distinguish between different types of depression.

In the Health 2000 Survey, the full version of the Munich CIDI (M-CIDI) was used to assess prevalence in adults 30 years and over (n=8028). The 12-month prevalence of MDD was 4.9%; dysthymia was 2.5%; and any depressive disorder was 6.5% (Pirkola *et al.*, 2005b). In these figures, non-participation was accounted for by using poststratification weights.

Incidence of depression in the general population was studied in Southwest Finland as part of the international ODIN study. The incidence rate for all depressive disorders was 28.5 / 1000 per year; for first-time episodes, it was 20.5 / 1000 (Lehtinen *et al.*, 2005).

In summary, the prevalence of depressive disorders in Finland is very close to the global average.

### 2.2.4 PREVALENCE OF DYSTHYMIA

Compared with MDD, fewer studies have investigated the prevalence of dysthymia. For the Global Burden of Disease 2010 study, a thorough systematic review found 38 studies, and established a period (combined current, 1-, 3-, 6- and 12-month) prevalence of 1.6% (Charlson *et al.*, 2013). Prevalences in different studies ranged from 0.0% to 8.5%. Data from many regions was lacking, and the estimate was partly based on modelling. Other reviews have found annual prevalences of 2.0% (Waraich *et al.*, 2004) and 0.1-1.5% (Gureje, 2011). National studies have found 0.5-1.5% 12-month prevalence rates in the United States (Blanco *et al.*, 2010); 0.9-2.5% in the Netherlands (Bijl *et al.*, 1998, de Graaf *et al.*, 2012); 1.1% in Australia (Andrews *et al.*, 2001); and 1.7% in Germany (Jacobi *et al.*, 2015).



## 2.2.5 THE GLOBAL BURDEN OF DEPRESSIVE DISORDERS

When only mortality is assessed, the impact of mental disorders on disease burden is largely underestimated. Historically, this has led to mental disorders being neglected within different public health priorities. The *World Development Report of 1993: Investing in Health* report introduced the Disability Adjusted Life Year (DALY) measure that made it possible to quantify, for the first time, the real impact of mental disorders on public health (Bank, 1993). This new focus on disability in addition to mortality has been of key importance in placing mental disorders on the global public health agenda.

The global burden of disease (GBD) is calculated as a function of prevalence, disability and deaths due to the disorder, and is expressed in DALYs. These are a sum of years of life lost due to premature mortality (YLL) and years lived with disability (YLD), a calculation that is based on the prevalence and disability caused by the condition.

In the GBD 2010 study, prevalence and epidemiological modelling was done for both MDD and dysthymia (Charlson *et al.*, 2013, Ferrari *et al.*, 2013a, Ferrari *et al.*, 2013c). For the disability weights, lay health state descriptions were presented in an online survey to nearly 15,000 lay participants from around the world. When 0 represents full health and 1 represents death, disability weights were assigned as follows: mild depression 0.16; moderate depression 0.41; severe depression 0.66; and dysthymia 0.16. Based on population surveys, it was estimated that 14% of people with depressive disorders are asymptomatic; 59% have a mild condition; 17% moderate; and 11% severe.

Globally, mental and substance use disorders are the leading cause of years lived with disability (YLD), causing 21.2% of all YLDs (Global Burden of Disease Study 2013 Collaborators, 2015). The burden of disability due to MDD (measured in YLD) increased by 53% between 1990 and 2013, but the age-standardised disability burden increased by only 4% (Global Burden of Disease Study 2013 Collaborators, 2015). The burden due to dysthymia increased by 55% without any significant change in age-standardised rate. When taking into account mortality and disability, the age-standardised rate of DALYs due to depressive disorders did not change significantly between 1990 and 2013 (Murray *et al.*, 2015). MDD ranks second (after lower back pain) as a contributor to the burden of years lived with disability (YLD), and accounts for 8.1% of all YLDs. Dysthymia is the 16th contributor and accounts for 1.3% (Global Burden of Disease Study 2013 Collaborators, 2015). Considering the impact of non-participation has on prevalence estimates, it is likely that the global burden of depression is even higher than currently estimated.

In the GBD 2010, mortality due to depressive disorders was modelled so that MDD was considered a risk factor for suicide (odds ratio (OR) 19.9) and ischemic heart disease (OR 1.6) (Ferrari *et al.*, 2013b). This meant that MDD accounted for 16 million DALYs (46%) due to suicides, and 3.8 million DALYs (2.9%) due to ischemic heart disease. However, these deaths were not included in the calculation of burden caused by depressive disorders. Had they been reattributed to MDD, the overall burden of MDD would have increased from 2.5% to 3.4% of global DALYs, ranking as the eighth instead of the eleventh cause (Ferrari *et al.*, 2013b).

There is substantial regional variation in the contribution of depressive disorders to the overall disease burden. For example, in the North African and Andean South American regions, depressive disorders are the third leading contributor to DALYs, whereas in different parts of Sub-Saharan Africa they are the 13th to 19th contributor, respectively, and in South Asia they are the 14th contributor (Ferrari *et al.*, 2013b). However, in the burden of disability (YLD) category, MDD is among the three most important contributors in all but a few countries globally, and in all countries it ranks among the top 10 (Global Burden of Disease Study 2013 Collaborators, 2015). In Finland, depressive disorders are the 6th leading contributor to DALYs.

## **2.3 PREVALENCE TRENDS OF DEPRESSIVE DISORDERS OVER TIME**

Through heightened awareness of depression among the general population, increased help-seeking and use of services, and certain topical issues (such as increased disability pensions due to depression), there is a widespread perception that depression has increased. Contrary to his perception however, no studies indicate this. Globally, the point prevalence of MDD has remained stable at 4.4% in 1990 and 2010 (Ferrari *et al.*, 2013c). There are few national studies where this has been assessed, but general population studies from the Netherlands, Canada, US and the UK have found no increase in the prevalence of depressive disorders from the 1950s to 2010s (Brugha *et al.*, 2004, de Graaf *et al.*, 2012, Kessler *et al.*, 2005, Murphy *et al.*, 2000, Patten *et al.*, 2015b). During this time, however, there have been changes in both the diagnostic criteria and study methodologies, which complicates the comparison of the studies.

## **2.4 RISK FACTORS FOR DEPRESSIVE DISORDERS**

Depressive disorders are multifactorial, and both genetic and environmental factors increase the risk of developing depression. With age, the importance

of environmental factors increases (Nivard *et al.*, 2015). There is evidence of a genetic risk, but efforts to identify the specific loci involved have so far failed. It is possible that the genetic contribution is smaller than expected, or that the disorder represents either different symptom clusters or different genetic pathways to the same symptomatic manifestation (Colman and Ataullahjan, 2010, Flint and Kendler, 2014, Kendler *et al.*, 2013).

Environmental correlates of depressive disorders, in particular MDD, have been studied extensively in cross-sectional studies. However, a factor or characteristic may be associated with current depression via two ways: by being a risk factor of incidence of the disorder; or by contributing to longer duration and thus increasing prevalence of depression in people with that characteristic (Lorant *et al.*, 2003). To understand the mechanisms of etiology and target preventive efforts, knowledge about the first type of associations would be essential. This can only be reliably assessed in longitudinal studies, which are more rare than cross-sectional studies.

In this literature review, primarily risk factors of incidence are reviewed. When correlates of prevalence are discussed, this will be specifically mentioned. The most important risk factors are summarised in Table 5.

## **2.4.1 SOCIODEMOGRAPHIC FACTORS**

### **2.4.1.1 Gender**

Depression is more common among women than men (Kessler and Bromet, 2013, Seedat *et al.*, 2009) and this is due to its higher incidence among women: women have an approximately 1.5 to 2-fold risk of developing depression compared with men (Anthony and Petronis, 1991, De Graaf *et al.*, 2002, Eaton *et al.*, 2001, Eaton *et al.*, 2008c, Klein *et al.*, 2013, Stegenga *et al.*, 2013, Wang *et al.*, 2010a). However, the reverse is true in prepubertal children, and the higher risk of women is observed only from puberty (12 years) onwards (Wesselhoeft *et al.*, 2015). The incidence of depression in women peaks at 20 years of age; and after 40 years of age, the incidence is close to that of men (Pedersen *et al.*, 2014).

Twin studies have been used to model the risk factors of major depression in men and women. They suggest that the risk of major depression results from three pathways in both men and women: internalising symptoms; externalising symptoms; and psychosocial adversity. In men, losing a parent as a child, low self-esteem and genetic risks were more important explanatory variables than in women. The authors pointed out, however, that the pathways in both genders were similar, and that the differences are of less importance than the similarities (Kendler *et al.*, 2002, 2006). In a

further study, the same group noted that for women, problems in caring relationships and interpersonal issues (such as lack of parental warmth, divorce, social support and marital dissatisfaction as well as neuroticism) were more important risk factors than for men (Kendler and Gardner, 2014). For men, stressful life events of financial, occupational or legal nature, as well as childhood sexual abuse, conduct disorder, drug abuse, and a prior history of depression were more important factors than for women.

Notably, the World Health Survey shows that the relative risk of women to men increases with increasing country income (Rai *et al.*, 2013). On the other hand, in the World Mental Health Survey, the difference between men and women decreased in the younger cohorts (Seedat *et al.*, 2009). They also found gender differences to be smaller in countries and cohorts with greater equality between male and female roles. An exception among countries is China, where some studies have found no gender differences in prevalence of depression (Bromet *et al.*, 2011, Lee *et al.*, 2009). A recent meta-analysis, however, did show a typical pattern of female dominance in depression (Gu *et al.*, 2013).

#### **2.4.1.2 Age**

Depression is more prevalent in younger age groups (Kessler and Bromet, 2013). In longitudinal studies, younger age has been established as a risk factor for developing depression (Eaton *et al.*, 2008c, Stegenga *et al.*, 2013, Wang *et al.*, 2010a). This association, however, is less clear, or sometimes even reversed, in low-income countries (Kessler and Bromet, 2013). When incidence of depression was examined in a register-based study in Denmark, it increased steeply from 10 years of age until 20 and then reduced, until there was another peak at 80-90 years of age (Pedersen *et al.*, 2014).

However, these findings should be interpreted with some caution, as there are challenges related to diagnosing depression among older persons using structured clinical interviews. Comparison of the CIDI, GHQ and K-10 in the Australian Mental Health Survey demonstrated that inconsistencies between the instruments rose with age (O'Connor and Parslow, 2009). It was interpreted that the complex questions of the CIDI may confuse older people and thus lead to an underestimation of mental disorders in the elderly (O'Connor and Parslow, 2010).

#### **2.4.1.3 Socioeconomic position**

There is a well-known cross-sectional association between lower socioeconomic position (SEP) and depressive disorders (Fryers *et al.*, 2003, Laurant *et al.*, 2003, Pulkki-Råbäck *et al.*, 2012). A systematic review of 51

prevalence studies found an OR 1.8 for prevalence of depression among the lowest versus the highest socioeconomic group.

However, the causality of the association is a subject of debate, and both causal pathways have evidence and a credible theory behind them. These are called the “causation” theory, where low SEP is a risk factor for depression, and the “selection” theory, where depression either prevents upward social mobility or causes downward movement (Dohrenwend *et al.*, 1992). In line with the “causation” theory, the stress hypothesis suggests that individuals with high SEP have better personal resources to cope with stress, such as self-esteem, coping style and locus of control, and are less prone to develop depression because of these resources (Lorant *et al.*, 2003).

It is important to note that three central confounders of the relationship between SEP and depression are gender, age and physical diseases. The latter is often ignored in the literature (Lorant *et al.*, 2003).

A meta-analysis of five longitudinal studies found only a slightly elevated risk of depression in the lowest SEP group (OR 1.2), whereas the risk of prevalent depression and persistence of disorder were higher (OR 1.8 and 2.0, respectively) (Lorant *et al.*, 2003). This was interpreted as supporting the “causation” theory, and in particular the “stress” theory of higher SEP as a protective factor, and in the event of falling ill with depression, a factor promoting recovery. Many individual longitudinal studies have found poverty to be associated only with persistence, not onset of depression (Skapinakis *et al.*, 2006, Weich and Lewis, 1998), although some have found an association with incidence of depression (Kosidou *et al.*, 2011).

It is most likely, however, that both processes occur simultaneously and interact (Lorant *et al.*, 2003). A further question, in context of the causation theory, is whether the influence of lower social status on adult depression results from lower SEP in adulthood, or whether the influence is a result of adversity earlier in life (Muntaner *et al.*, 2004). Again, it is likely that lower SEP both during childhood and adulthood increase the risk of depression.

Of the different indicators of socioeconomic status, associations have been found with educational status and employment status, as well as income or material assets (Fryers *et al.*, 2003). The relationship with education might be weaker and in many cases non-existent (Andersen *et al.*, 2009, Kosidou *et al.*, 2011). The Canadian NPHS study found very differing results according to employment status: lower education was associated with increased risk of developing depression among those who worked, but lower risk among those who did not work (Wang *et al.*, 2010b).

In addition, financial hardship, such as having to go without meals or heating, is associated with current depression, independently of other measures of SEP (Butterworth *et al.*, 2009, Dijkstra-Kersten *et al.*, 2015, Lahelma *et al.*, 2006, Wang *et al.*, 2010b, Weich and Lewis, 1998). However, the association is cross-sectional, and it is unclear whether it predicts new-onset depression, with both positive findings (Skapinakis *et al.*, 2006, Wang *et al.*, 2010b, Weich and Lewis, 1998) and negative ones (Butterworth *et al.*, 2009, Dijkstra-Kersten *et al.*, 2015) from longitudinal studies. The causality here may be in the other direction: people suffering from depression may be more likely to experience either true or perceived financial strain.

#### **2.4.1.4 Marital status**

Depression is more prevalent among those who are divorced, separated or never-married (Kessler and Bromet, 2013). In the WMHS, being married was associated with reduced risk of onset of depression in men, but not in women (Scott *et al.*, 2010). Being separated or divorced was associated with increased risk in both genders. Some other studies have also found an increased risk of developing depression among the unmarried (Anthony and Petronis, 1991), or specifically, those who separated during the follow-up period (Lorant *et al.*, 2007).

However, many studies have not found a significant association between marital status and the risk of developing depression. Therefore, it may be that marital status influences the course of illness, or that the causal pathway is reversed.

### **2.4.2 FAMILY HISTORY AND EARLY LIFE EXPERIENCES**

#### **2.4.2.1 Family history**

A meta-analysis of the genetic epidemiology of depression found a 2.8-fold risk in first-degree relatives of people with major depression. The heritability, or the proportion of variation in the population explained by genetic variation, is estimated at 37% (Sullivan *et al.*, 2000).

#### **2.4.2.2 Early life experiences**

Many factors and experiences during childhood and adolescence have been established as risk factors for developing depression (Kendler *et al.*, 2002) (Kendler *et al.*, 2006). The risks start accumulating from the very beginning of life: low birth weight, but not premature birth, is a risk factor for depression (Loret de Mola *et al.*, 2014).

Childhood adversities – such as low parental education (Park *et al.*, 2013, Ritsher *et al.*, 2001), parental depression (Eaton *et al.*, 2001, Klein *et al.*, 2013) or any parental mental disorder (Pirkola *et al.*, 2005a, Stegenga *et al.*, 2013), exposure to bullying (Bowes *et al.*, 2015, Sourander *et al.*, 2015) and family discord (Pirkola *et al.*, 2005a), or physical, emotional or sexual abuse (Chen *et al.*, 2014, Stegenga *et al.*, 2013) – are well-known risk factors for depression. The accumulation of several adversities increases the risk (Elovainio *et al.*, 2015, Pirkola *et al.*, 2005a). The impact of childhood adversity might be more apparent in women than in men (Veijola *et al.*, 1998).

However, childhood adversities and other early life experiences are frequently ascertained retrospectively, and people often report them inconsistently. Recently, it was demonstrated that current depression and stress were associated with remembering childhood adversities that the individual had not reported in an earlier interview, and not forgetting the adversities previously reported, both indicating memory bias related to current depression (Colman *et al.*, 2015).

Finally, threatening and other stressful events during adult life increase the risk of incident depression (Lehtinen *et al.*, 2005), and adult and childhood stressful events are also associated with each other (Kendler *et al.*, 2002). When these events, such as financial problems, robbery or work problems, are separated into those dependent on the individual's behaviour and those independent of that behaviour, both types predict depression (Kendler *et al.*, 2002, 2006).

### 2.4.3 SOCIAL CAPITAL

Social capital refers to the collective value of the social networks possessed by an individual. In a Finnish study, factor analysis was used to condense several variables indicating aspects of social capital into three dimensions: social support; social participation and networks; and trust and reciprocity (Nieminen *et al.*, 2008). The same dimensions have also been identified in other studies and expert groups (Zukewich and Norris, 2005). There was a strong association between trust and participation dimensions and psychological well-being (Nieminen *et al.*, 2010).

There is extensive literature on the association between social capital and mental health, and in particular depression, at both the individual (De Silva *et al.*, 2005, Forsman *et al.*, 2012, Jones *et al.*, 2014, Nyqvist *et al.*, 2013) and population level (Smith and Kawachi, 2014). A summary measure of low social integration correlated with increased suicide risk among women in the



US (Tsai *et al.*, 2015). With few exceptions, these associations have been established cross-sectionally.

One study looked specifically at social capital and risk of depression in a prospective setting and found that the increased risk of depression among people with low social trust was explained by baseline depression (Fujiwara and Kawachi, 2008). The Dutch NESDA study also did not find any measure of social support (having a partner, network size, perceived emotional support) to predict new depressive episodes when controlled for personality features and clinical characteristics (Noteboom *et al.*, 2015). However, other longitudinal studies have identified social isolation (Kaplan *et al.*, 1987), lack of social support (Stegenga *et al.*, 2013) and decreased social participation (Kivelä *et al.*, 1996) to predict the onset of depression.

#### **2.4.4 CHRONIC SOMATIC CONDITIONS AND HEALTH BEHAVIOURS**

Many chronic diseases have high comorbidity with depression. Having a chronic physical disease predicts the onset of depression (Kaplan *et al.*, 1987, Patten, 2001, Stegenga *et al.*, 2013, Wang *et al.*, 2010a). In addition to chronic diseases, traumas, such as traumatic brain injuries, also increase the risk of depression (Perry *et al.*, 2016). People with chronic somatic disorders may also have a longer course of illness. This, together with increased incidence, results in a higher prevalence of depression among people with chronic somatic disorders (Patten, 2005). The association may be directly causal, as in the case of hypothyroidism, or it may be that the experience of living with a chronic illness contributes to developing depression. Common causal pathways, such as inflammation, have also been investigated (Kiecolt-Glaser and Glaser, 2002). The association between chronic somatic conditions and depression is bidirectional, so that depression is also a risk factor for many somatic conditions, and worsens their prognosis (see 2.6.5).

In a recent meta-analysis, both obesity (adjusted OR 1.6) and being overweight (adjusted OR 1.08) predicted the onset of depression (Luppino *et al.*, 2010). High consumption of processed foods is also a risk factor for later development of depressive symptoms, whereas a diet rich in vegetables, fruit and fish is a protective factor (Akbaraly *et al.*, 2009). The Mediterranean diet and consumption of fruits and nuts, unsaturated fatty acids and legumes, in particular, seems to be protective against depression (Sanchez-Villegas *et al.*, 2009). In addition, leisure time physical activity unrelated to occupational activity appears to protect against psychological distress in men (Wiles *et al.*, 2007). A systematic review of diet and depression confirmed these findings, but methodological limitations of the studies and their limited evidence base raise cautions against making firm conclusions (Rahe *et al.*, 2014).



Both alcohol use and alcohol use disorder (AUD) are associated with an increased risk of depression, of up to twofold in diagnosed AUDs (Boden and Fergusson, 2011). Cannabis use is also associated with an increased risk of depression, and there is a dose-response where heavy use (OR 1.6) implies a higher risk than light use (OR 1.2) (Lev-Ran *et al.*, 2014).

Finally, the association between smoking and depression is strong and well-known. A systematic review of longitudinal studies concluded that the risk of developing depression among adolescent smokers was 1.7-fold, and the risk of taking up smoking among depressed adolescents 1.4-fold (Chaiton *et al.*, 2009). Also among adult smokers, the risk of developing depression is twofold, and smoking cessation could reduce this risk (Bakhshaie *et al.*, 2015, Pasco *et al.*, 2008). A twin modelling study concluded that there is both a causal relationship between nicotine dependence and development of depression and a shared genetic risk (Edwards and Kendler, 2012).

#### **2.4.5 OTHER PSYCHIATRIC DISORDERS AND PERSONALITY TRAITS**

Because there is some diagnostic overlap and common risk factors between depressive and other psychiatric disorders, it is understandable that the latter are also risk factors for developing depression. Anxiety disorders in particular are a risk factor for later onset of depression (Eaton *et al.*, 2008c, Klein *et al.*, 2013, Stegenga *et al.*, 2013). Comorbidity with anxiety disorders may vary according to the diagnostic thresholds used, with lower diagnostic thresholds for MDD increasing comorbidity (van Loo *et al.*, 2015b).

Personality traits such as neuroticism also increase the risk of depression (De Graaf *et al.*, 2002, Noteboom *et al.*, 2015). A low sense of coherence, harm-avoidance and low self-esteem are associated with increased incidence of depression (Lehtinen *et al.*, 2005, Luutonen *et al.*, 2011, Miettunen *et al.*, 2012, Miettunen and Raevuori, 2012).

Subclinical depressive symptoms and general psychological distress (Ernst *et al.*, 1992, Horwath *et al.*, 1992, Klein *et al.*, 2013, Skapinakis *et al.*, 2006), as well as sleep problems (De Graaf *et al.*, 2002, Riemann and Voderholzer, 2003) indicate a risk of developing depression. It can be questioned whether these represent an independent risk factor or a marker of a premorbid state of depressive disorder.

Finally, it is important to note that accumulation of several risk factors further increases the risk of depression (Meng and D'Arcy, 2014).

**Table 5.**      *Established risk factors of depressive disorders in longitudinal population studies*

<b>Genetic and early life</b>		
Biological factors	Female sex	(Anthony and Petronis, 1991, De Graaf <i>et al.</i> , 2002, Eaton <i>et al.</i> , 2001, Eaton <i>et al.</i> , 2008c, Klein <i>et al.</i> , 2013, Stegenga <i>et al.</i> , 2013, Wang <i>et al.</i> , 2010a)
	Genetic risk	(Flint and Kendler, 2014)
Early life and family	Low parental education and occupational position	(Park <i>et al.</i> , 2013, Ritsher <i>et al.</i> , 2001)
	Physical or sexual abuse	(Stegenga <i>et al.</i> , 2013)
	Family history of MDE	(Eaton <i>et al.</i> , 2001, Klein <i>et al.</i> , 2013, Stegenga <i>et al.</i> , 2013, Wang <i>et al.</i> , 2010a)
	Younger age	(Eaton <i>et al.</i> , 2008c, Stegenga <i>et al.</i> , 2013, Wang <i>et al.</i> , 2010a)
<b>Adulthood</b>		
Personality	Neuroticism	(De Graaf <i>et al.</i> , 2002, Noteboom <i>et al.</i> , 2015)
	Harm avoidance	(Miettunen <i>et al.</i> , 2012)
Socio-economic position	Unemployment	(Anthony and Petronis, 1991, Stegenga <i>et al.</i> , 2013)
	Financial strain	(Lorant <i>et al.</i> , 2007, Skapinakis <i>et al.</i> , 2006, Stegenga <i>et al.</i> , 2013, Wang <i>et al.</i> , 2010b, Weich and Lewis, 1998)
	Low education	(Wang <i>et al.</i> , 2010b)(in the working population) (Stegenga <i>et al.</i> , 2013)
	Low income (among non-working population and working men)	(Wang <i>et al.</i> , 2010b)
Social capital and relationships	Separated or divorced	(Anthony and Petronis, 1991, Lorant <i>et al.</i> , 2007, Stegenga <i>et al.</i> , 2013)
	Social isolation	(Kaplan <i>et al.</i> , 1987)
	Low social participation	(Kivelä <i>et al.</i> , 1996)
	Negative life events	(De Graaf <i>et al.</i> , 2002, Eaton <i>et al.</i> , 2001)
	Problems with neighbourhood	(Stegenga <i>et al.</i> , 2013)
	Low social support	(Stegenga <i>et al.</i> , 2013)
Other psychiatric disorders	Depressive symptoms	(Ernst <i>et al.</i> , 1992, Horwath <i>et al.</i> , 1992, Klein <i>et al.</i> , 2013, Skapinakis <i>et al.</i> , 2006, Stegenga <i>et al.</i> , 2013)
	Sleep problems	(De Graaf <i>et al.</i> , 2002)
	Anxiety disorders, substance use and other psychiatric disorders	e.g. (Eaton <i>et al.</i> , 2008c, Stegenga <i>et al.</i> , 2013)
Poor physical health	Poor perceived health	(Kaplan <i>et al.</i> , 1987)
	Chronic somatic conditions	(Kaplan <i>et al.</i> , 1987, Patten, 2001, Stegenga <i>et al.</i> , 2013, Wang <i>et al.</i> , 2010a)

## 2.5 PROGNOSIS OF DEPRESSIVE DISORDERS

The average duration of a major depressive episode in population studies is 3-4 months (Eaton *et al.*, 2008b, Kessler *et al.*, 2003, Spijker *et al.*, 2002), but 15-20% have a chronic course of illness, lasting years (Eaton *et al.*, 2008b, Spijker *et al.*, 2002). Based on an extensive literature review, the GBD study modelled the average episode duration of 37.7 weeks (8.7 months) for MDD (Ferrari *et al.*, 2013a).

Dysthymia is a long-term illness. Although its duration is less well known than MDE, the median time to recovery is counted in years, not months (Klein *et al.*, 2006). In its review, the GBD study found insufficient data to model duration and remission (Charlson *et al.*, 2013).

### 2.5.1 KEY CONCEPTS OF PROGNOSIS

#### 2.5.1.1 *Remission, recovery and recurrence*

In a landmark paper from 1991, a task force of the MacArthur Foundation Research Network on the Psychobiology of Depression (Frank *et al.*, 1991), proposed definitions of key concepts of major depressive disorder as follows:

*Remission*: a brief period (x to z days) during which the individual no longer meets syndromal criteria for the disorder and has only minimal symptoms.

*Recovery*: Remission that has lasted z+1 days or longer. The concept refers to recovery from the episode, not the illness itself.

*Relapse*: Return of symptoms that meet the syndrome criteria during the period of remission, but before recovery. Conceptually a relapse represents the return of the symptoms of a still ongoing episode.

*Recurrence*: Appearance of a new episode of the disorder during recovery.

The concept of “asymptomatic” can be operationalised as having 8 points or less on the BDI (21 questions) scale; 7 or less on the Hamilton Rating Scale for Depression; or a maximum of 2 symptoms on the Schedule for Affective Disorders and Schizophrenia (Frank *et al.*, 1991).

Frank *et al.* (1991) provide various suggestions for the time limits of remission and recovery. Suggested minimum duration for remission is 2 to 3 weeks, whereas the maximum duration, and limit to recovery, could be 2-6

months. In a later analysis, 2 months was considered too short, as more than half of those in remission at 2 months still experienced a relapse within 18 months. 4 or 6 months was recommended as the limit between remission and recovery (Furukawa *et al.*, 2008).

In the case of dysthymia, the GBD 2010 study defined remission as no longer meeting diagnostic criteria over a follow-up period of minimum 2 years (Charlson *et al.*, 2013), but the concepts are less clearly defined than for MDD.

### **2.5.1.2 Residual symptoms and psychosocial disability**

Residual symptoms or subthreshold symptoms refer to symptoms of depressive disorder that persist after an episode, when either the number or intensity of symptoms no longer meet diagnostic criteria. Sub-threshold symptoms are also associated with psychosocial disability (Judd *et al.*, 2000).

Lowered psychosocial functioning is frequently found after a depressive episode, which could, in theory, result from three sources: residual symptoms; a permanent scarring effect; or a trait vulnerability that pre-existed the depressive episode. Ormel *et al.* (2004) tested these hypotheses and found evidence both for trait effect, meaning that the premorbid psychosocial functioning was already lower among persons who later developed depression, and state effect, meaning that psychosocial functioning worsened significantly during the depressive episode and was related to symptom severity. Scarring, a low psychosocial functioning in the absence of depressive symptoms, only occurred in severe recurrent depression.

In addition, cognitive impairment in the fields of executive function and attention often persists after remission from depression (Rock *et al.*, 2014), although the cognitive impairment resulting from depression may be smaller in population samples than in clinical studies (Castaneda *et al.*, 2008). Impaired cognition may in turn cause problems in psychosocial functioning (Papakostas and Culpepper, 2015).

## **2.5.2 REMISSION, RECOVERY AND RECURRENCE IN POPULATION STUDIES**

Many of the longitudinal studies of general population samples that examine prognosis of depressive disorders were carried out several decades ago with now outdated methodology. In the Stirling County study, which began in

1952 and was followed up for 17 years, 75% of cases with baseline depression had a poor outcome or subsequent episodes, and 26% had a chronic course of illness (Murphy *et al.*, 1986). The Zurich cohort study followed up a cohort of 19 to 20-year-olds, and found that 47% of those with baseline depression received no diagnosis at any of the follow-ups during seven years (Vollrath and Angst, 1989). The Upper Bavarian Longitudinal Community Study followed a rural population in Bavaria, Germany, and found that, after 25 years, 20% of those with pure depression at baseline still had depression, and 73% had no depression or anxiety disorder (Fichter *et al.*, 2010). A Swedish study with a very long follow-up of 30-49 years, found a recurrence rate of 40%, and transition to other diagnoses in 21% of the sample (Mattisson *et al.*, 2007).

In the more recent population studies, the prognosis seems somewhat better. In the Netherlands, 21% of persons with pure (not comorbid) depressive disorder, and 35% of those with comorbid disorder, still had a depressive disorder at the seven-years follow-up (Rhebergen *et al.*, 2011). In Canada, 77% of persons with MDE had recovered by the 2-year follow-up (Fuller-Thomson *et al.*, 2014).

Recovery rates in clinical studies have generally been lower than in population studies, with 45-50% at 2 to 5-year follow-up. (Holma *et al.*, 2008, Penninx *et al.*, 2011, Stegenga *et al.*, 2012). In a study of Finnish primary care patients with MDD, the median time to remission was 20 months (Riihimäki *et al.*, 2014).

Also, when symptom scores such as the BDI are used as outcome measures, recovery rates are lower. Two studies in general populations in Finland found recovery, defined as non-symptomatic in the BDI scale, in 35% of the sample over a 2-year follow-up and in 46% over 9 years (Dowrick *et al.*, 2011, Viinamäki *et al.*, 2006b).

It is commonly believed that approximately 50% of persons with a first depressive episode will have a recurrent episode. This figure may be lower in the general population and higher when specialised mental health care settings are studied (Hardeveld *et al.*, 2010). In a Dutch general population sample, 13% had a recurrent episode within five years; 23% in 10 years; and 42% in 20 years (Hardeveld *et al.*, 2013).

Dysthymia is considered a chronic, as opposed to episodic, disorder. In a 10-year follow-up of patients with dysthymia, 74% achieved recovery, but 71% of them had a relapse. Median time to recovery was 52 months (Klein *et al.*, 2006). In a general population study, 65% of persons with initial chronic depression had recovered at three years (Agosti, 2014).

### **2.5.3 QUALITY OF LIFE IN PEOPLE RECOVERED FROM DEPRESSION**

During the symptomatic phase, persons with depressive disorders experience significant reductions in health-related quality of life (Saarni *et al.*, 2007). It is unclear how much of this reduction persists after symptomatic recovery from the disorder. In a 6-year follow-up study, patients with initial depression achieved normal mood, functional capacity and life satisfaction (Koivumaa-Honkanen *et al.*, 2008). On the other hand, in another 6-year follow-up study, women who recovered from depression continued to have lower health-related quality of life in the fields of social functioning and pain. Some of the association was mediated by sleep disturbance, which was an independent predictor of low health-related quality of life (Joffe *et al.*, 2012). Finally, in an elderly population, there was a surprising temporal association between reduction in HRQoL and subsequent depressive symptoms, but not in the opposite direction (Hajek *et al.*, 2015).

### **2.5.4 PREDICTORS OF DIFFERENT NEGATIVE OUTCOMES**

Knowledge of factors that predict negative outcomes, such as chronicity, recurrence, higher disability or mortality in depressive disorders, could in theory be used to target more intensive treatment interventions to these high-risk groups. Attempts have been made to find markers that predict treatment response to antidepressants, but have so far produced few results that are applicable to clinical practice (Kuk *et al.*, 2010).

#### **2.5.4.1 Individual characteristics**

The evidence on the impact of age and gender on prognosis of depressive disorders is inconclusive. Some studies have found younger persons to have a higher risk of non-recovery or recurrence (Eaton *et al.*, 2008b, Holma *et al.*, 2008) while older age appears to be an indicator of chronicity in dysthymia in particular (Agosti, 2014, Klein *et al.*, 2008, Penninx *et al.*, 2011). Some studies have found women to have a worse prognosis (Spijker *et al.*, 2001), but most have found no difference between genders. Being single (divorced, separated, never-married or widowed) is a consistent predictor of unfavourable outcomes (Agosti, 2014, Eaton *et al.*, 2008b, Mueller *et al.*, 1999). Worsening of the economic situation during the follow-up is also associated with persistence of depressive symptoms (Viinamäki *et al.*, 2006a).

Childhood adversities, in particular different forms of abuse, have been associated with longer duration of depressive symptoms, persistence and recurrence (Agosti, 2014, Dowrick *et al.*, 2011, Fuller-Thomson *et al.*, 2014, Gilman *et al.*, 2013, Klein *et al.*, 2008, Nanni *et al.*, 2012, Rhebergen *et al.*,

2011). Possible explanations for this, as suggested by Gilman *et al.* (2013), are that psychosocial stressors and their sequelae increase vulnerability to the impact of stress on psychopathology, and may also reduce the effectiveness of psychological treatments. Accumulation of several traumatic events during adult life is also associated with persistence of depressive symptoms (Tanskanen *et al.*, 2004). Family history of depression, which may indicate both genetic risk and impact on childhood experiences, is another risk factor of persistence of depression (Dowrick *et al.*, 2011).

Despite the well-documented cross-sectional relationship between social capital and depression, few studies have investigated the impact of social capital on prognosis of depression. In a clinical setting, low social support and adverse life events were associated with more depressive symptoms at follow-up (Leskelä *et al.*, 2006).

#### **2.5.4.2 Disorder characteristics**

The severity of the disorder is closely related to its outcomes, with more severe disorders (measured with symptom scales or according to DSM-defined diagnostic criteria) and those with psychotic features being more persistent (Penninx *et al.*, 2011, Spijker *et al.*, 2001, Spijker *et al.*, 2002, Viinamäki *et al.*, 2006a). Psychiatric comorbidity, especially with anxiety and personality disorders, is also related to worse outcomes (Agosti, 2014, Holma *et al.*, 2008, Klein *et al.*, 2008, Murphy *et al.*, 1986, Patten *et al.*, 2010, Penninx *et al.*, 2011, Rhebergen *et al.*, 2011, Spijker *et al.*, 2001, Spijker *et al.*, 2002, Viinamäki *et al.*, 2006a). Personality traits such as neuroticism also predict worse outcomes (Rhebergen *et al.*, 2009, Spijker *et al.*, 2001). Finally, cognitive symptoms of depression, such as memory impairment and attention difficulties, have an adverse impact on the course of illness (McIntyre *et al.*, 2013, Papakostas, 2014, Trivedi and Greer, 2014). Specifically, autobiographical memory deficits have been associated with recurrent depression (Talarowska *et al.*, 2016).

In terms of recurrence, the number of earlier episodes is the strongest predictor of a recurrent episode (Bulloch *et al.*, 2014, Dowrick *et al.*, 2011, Hardeveld *et al.*, 2010). Regarding subtypes of depression (melancholic and atypical), it appears that severity is a more important predictor of outcomes than the subtype, although suicidal thoughts may persist longer in the melancholic subtype (Lamers *et al.*, 2016).



## **2.6 EXCESS MORTALITY IN DEPRESSIVE, ANXIETY AND ALCOHOL USE DISORDERS**

Most psychiatric disorders have increased mortality, and the pooled all-cause mortality risk for all mental disorders is twofold compared to the general population (Walker *et al.*, 2015). Two-thirds of these deaths are due to natural causes, and one-third to unnatural or unknown causes. With 14% of all global deaths attributable to mental disorders, they rank among the most important causes of mortality, contrary to what was previously believed (Walker *et al.*, 2015). Most of the evidence is from high-income countries, but identical findings in terms of mortality risk and years of life lost are reported from low-income countries (Fekadu *et al.*, 2015).

In a meta-analysis, the median of years of life lost due to mental disorders is 10 years (Walker *et al.*, 2015), but higher figures, from 10-20 years, have been reported for any psychiatric disorder (Chang *et al.*, 2011, Wahlbeck *et al.*, 2011) and up to 28.5 years for schizophrenia (Olfson *et al.*, 2015). In Finland, the gap in schizophrenia is somewhat smaller, at 16-17 years (Laursen *et al.*, 2013).

In a recent meta-analysis, the risk was highest for psychotic disorders (RR 2.5) and lowest for anxiety disorders (RR 1.4) (Walker *et al.*, 2015). Significantly higher risks have been reported for instance in personality disorders (SMR 5-6) (Björkenstam *et al.*, 2015) and schizophrenia (SMR 3.7) (Olfson *et al.*, 2015). However, the increased mortality is observed in all categories of mental disorders (Harris and Barraclough, 1998).

Fortunately, there are indications that, in the Nordic countries, the mortality gap between people with mental disorders and the general population is decreasing (Gissler *et al.*, 2013, Wahlbeck *et al.*, 2011).

### **2.6.1 EXCESS MORTALITY IN MAJOR DEPRESSIVE DISORDER**

Four recent extensive reviews have assessed excess mortality in major depressive disorder. First, the Global Burden of Disease study, based on its literature review, used an excess mortality risk of 1.9 in its epidemiological modelling (Ferrari *et al.*, 2013a). Second, a meta-analysis of 21 population-based studies found an RR of 1.91 in MDD (Baxter *et al.*, 2011). Third, in a meta-analysis of 203 studies covering different mental disorders, the mortality risk for depression was 1.7-fold (Walker *et al.*, 2015).

A fourth large meta-analysis of 293 studies (Cuijpers *et al.*, 2014a) found a relative mortality risk of 1.64, which decreased to 1.52 when corrected for publication bias. This was lower than the RR 1.8 reported in an earlier meta-



analysis of the same research team (Cuijpers and Smit, 2002). This study found that the longer the follow-up and the better the quality of the study, the lower the reported mortality risk. Cuijpers *et al.* therefore concluded that there is an elevated mortality risk in MDD, but this may have been exaggerated by publication bias and low-quality studies.

Many good-quality individual studies and earlier reviews have found hazard ratios close to those reported in the recent meta-analyses, which are 1.5 to 1.9 (Eaton *et al.*, 2008a, Leinonen *et al.*, 2014, Mykletun *et al.*, 2009, Penninx *et al.*, 1999). However, a large study of the Veterans Health Administration in the US found only a 17% increased risk, which was considered partially explained by the higher overall mortality of the studied group (Zivin *et al.*, 2015). Moreover, two large nationally representative community studies from North America did not find any independent risk after adjusting for sociodemographic differences, health behaviour and somatic health status (Everson-Rose *et al.*, 2004, Patten *et al.*, 2011).

Most of the deaths are due to natural causes, but the relative risk is higher for unnatural deaths (Hiroeh *et al.*, 2008, Walker *et al.*, 2015). Increased risk has been found for circulatory diseases, respiratory diseases, diabetes, influenza and septicaemia (Leinonen *et al.*, 2014, Nabi *et al.*, 2010a, Zivin *et al.*, 2015). Of unnatural deaths, the risk is increased not only for suicide (Leinonen *et al.*, 2014, Nock *et al.*, 2009, Zivin *et al.*, 2015), but also other unnatural causes, such as homicide and accidents (Crump *et al.*, 2013a, b). Cancer mortality appears not to be increased among the depressed (Leinonen *et al.*, 2014, Zivin *et al.*, 2015).

It is unclear whether some subgroups of depressed people have higher mortality than others. However, a recent meta-analysis showed a higher risk among men (HR 2.0) than women (HR 1.6) (Cuijpers *et al.*, 2014b). This was also found in a meta-analysis of studies among the elderly (Saz and Dewey, 2001).

## **2.6.2 EXCESS MORTALITY IN DYSTHYMIA**

There is a paucity of information about excess mortality in dysthymia. A literature review from 1998 found four studies reporting mortality risk in dysthymia. Combining the results, the overall risk of death was not increased, but the risk of unnatural causes was 4.5-fold, whereas the risk of natural death was 0.8-fold (Harris and Barraclough, 1998). More recently, the literature review carried out for the Global Burden of Disease 2010 study found only one meta-analysis, which consisted of two studies. No excess mortality in dysthymia was found (RR 1.37 95% CI 0.93–2.00) (Baxter *et al.*, 2011).

### 2.6.3 EXCESS MORTALITY IN ANXIETY DISORDERS

Even though anxiety disorders are as common as depressive disorders, their impact on mortality is much less studied. A meta-analysis of mental disorders and mortality found a 1.4-fold risk of all-cause mortality in anxiety disorders, the lowest among the mental disorders studied (Walker *et al.*, 2015). Another meta-analysis reports an RR 1.9 for panic disorder based on four studies, and insufficient data for other anxiety disorders (Eaton *et al.*, 2008a). An earlier systematic review found two studies that reported no increase in all-cause mortality, but significant increase in unnatural deaths in anxiety neurosis (Harris and Barraclough, 1998). In panic disorder, all-cause mortality was twofold.

Individual studies have found more mixed results. A population-based study in Norway found no increase in mortality after controlling for confounders. Interestingly, comorbid anxiety reduced the mortality risk in depression (Mykletun *et al.*, 2009). Similarly, a study of elderly with anxiety and depression found no increased mortality associated with anxiety (Holwerda *et al.*, 2007). In the Netherlands, however, anxiety was associated with 1.7-fold mortality risk in men but not in women (van Hout *et al.*, 2004) in one study, and 1.8-fold risk in women in another study (Denollet *et al.*, 2009). In the US, the risk was elevated for both men and women (Ostir and Goodwin, 2006). Of the specific anxiety disorders, generalised anxiety disorder (GAD) is associated with an increased cardiovascular mortality risk, even when controlled for comorbid depressive disorder (Martens *et al.*, 2010).

### 2.6.4 EXCESS MORTALITY IN ALCOHOL USE DISORDERS

According to earlier meta-analyses, mortality in alcohol use disorders (alcohol abuse and alcohol dependence) is 1.8 to 2-fold (Eaton *et al.*, 2008a, Harris and Barraclough, 1998). A recent meta-analysis of 81 studies found a twofold risk in general population studies, and a 3.4 to 4.6-fold increase in clinical samples (Roerecke and Rehm, 2013). Similarly, another new meta-analysis of 39 studies found a high mortality risk ratio, of 3.45, compared to the general population, without distinguishing between different samples (Laramée *et al.*, 2015). Few general-population studies have investigated mortality in alcohol use disorders controlling for confounders. A 14-year follow-up of a general population sample in Germany found 4.6-fold mortality in women and 1.9-fold in men (John *et al.*, 2013). In Finland, mortality was 1.6-fold among persons with alcohol dependence and 20-fold in alcohol-induced psychosis (Perälä *et al.*, 2010).

## **2.6.5 POSSIBLE MECHANISMS OF EXCESS MORTALITY**

Several mechanisms have been proposed to explain the excess mortality in depression, such as increased suicide rates and other unnatural deaths, unhealthy behaviours, biological dysregulation, poor access to or non-compliance with medical treatment, and iatrogenic effects of psychiatric medications. However, the quality of evidence for these mechanisms varies, and even the causal directions of some of them are unclear (Cuijpers and Schoevers, 2004, Thornicroft, 2011).

### **2.6.5.1 Suicide and other unnatural deaths**

In a Swedish longitudinal study with 50 years follow-up, the lifetime suicide risk for persons with affective disorders was 6%, much higher than the 0.3% of the population without mental disorders (Holmstrand *et al.*, 2015). In men, the risk was 8.4-fold and in women 2.6-fold compared to the population without mental disorders. In a Danish register-based study with median follow-up of 18 years, 6.7% of depressed men and 3.8% of depressed women committed suicide during the follow-up (Nordentoft *et al.*, 2011). Among people with depression, men, those with more severe depression, hopelessness, previous suicide attempts and psychiatric comorbidities have a higher suicide risk (Hawton *et al.*, 2013). Suicides account for 12-13% of the excess deaths among depressed outpatients (Moustgaard *et al.*, 2013). Suicide attempts are much more frequent than completed suicides. In a follow-up of depressed patients treated in secondary care, there were 10 attempts per 100 patients annually, although many patients had more than one attempt (Holma *et al.*, 2010).

In addition to suicide, the risk of homicidal death is 2.6-fold and the risk of accidental death 2.2 to 2.5-fold (Crump *et al.*, 2013a, b). However, even though the risk of unnatural deaths is increased, in absolute terms they account for a minority of all deaths.

### **2.6.5.2 Depression and coronary heart disease**

As discussed in 2.4.4, links between depression and many somatic diseases are bidirectional. Depressed persons have a 30% increased risk of both coronary heart disease and myocardial infarction (Gan *et al.*, 2014). Among patients with acute coronary heart syndrome, depression is an independent risk factor for adverse outcomes such as all-cause and cardiac mortality (Lichtman *et al.*, 2014, Whooley and Wong, 2013). Both behavioural (e.g. physical inactivity, medication nonadherence, smoking, poor diet and social isolation) and biological mechanisms (autonomic nervous system activation, systemic inflammation, activation of the HPA axis, stress-induced ischemia,

platelet activation, endothelial dysfunction and common genetic risk factors) are listed as potential mechanisms. According to some trials, antidepressant medication potentially improves cardiac outcomes (Whooley and Wong, 2013).

In addition to heart disease, MDD is a risk factor for other physical diseases. In the WMHS study, MDD predicted onset of all of the ten somatic conditions studied, including arthritis, diabetes, asthma, peptic ulcer and cancer (Scott *et al.*, 2015).

### **2.6.5.3 Hazardous health behaviours**

The association with many hazardous health behaviours and depression is bi-directional. These behaviours increase the risk of depression, as described in 2.4.4, and depression increases the risk of taking up or continuing such behaviours.

As noted before, there is a two-way association between smoking and depression. Depressed persons have a higher risk of taking up smoking (Chaiton *et al.*, 2009), and a 2-3 fold risk of relapse after quitting smoking (Zvolensky *et al.*, 2015). In addition, there might be risk factors that increase the likelihood of both smoking and depression (Boden *et al.*, 2010, Dierker *et al.*, 2002, Edwards and Kendler, 2012). Alcohol consumption is also higher among depressed persons (Cuijpers and Schoevers, 2004). In fact, in a study of 40-64-year old Finnish people, alcohol-related causes of death accounted for 50% of the excess mortality in depressed men, and 30% in women (Moustgaard *et al.*, 2013).

Besides smoking, depression is associated with unhealthy diets, higher body-mass index, metabolic syndrome, lower HDL cholesterol and reduced physical activity, all of which directly contribute to mortality (Cuijpers and Schoevers, 2004, Lehto *et al.*, 2008a, Lehto *et al.*, 2008b). Those with more severe symptoms and comorbidities are more likely to experience major weight gain (Heiskanen *et al.*, 2013). All of these health behaviours are also risk factors for depression (Luppino *et al.*, 2010, Wiles *et al.*, 2007).

It has been suggested that the link between depression and many of its behavioural and other physical risk factors is a systemic inflammatory process (Berk *et al.*, 2013, Kiecolt-Glaser *et al.*, 2015). Psychosocial stressors, for example, increase levels of pro-inflammatory cytokines (Berk *et al.*, 2013, Kiecolt-Glaser *et al.*, 2015). In addition, sleep deprivation, poor diet and lack of exercise impact both immune function and systemic inflammation, and obesity itself is a state of systemic inflammation (Berk *et al.*, 2013). These pathways are closely related to increased mortality, as discussed below.

#### **2.6.5.4 Biological dysregulation**

Three main biological mechanisms have been proposed to explain the higher somatic morbidity and mortality among persons with depression: neuro-immune dysregulation, hyperactivity of the HPA axis, and sympathoadrenergic dysregulation. However, the causal and temporal relationship between these mechanisms and depression is not entirely clear (Cuijpers and Schoevers, 2004).

First, depression can stimulate the production of proinflammatory cytokines, which may in turn increase the risk of cardiovascular disease, diabetes, osteoporosis, arthritis and some cancers (Cuijpers and Schoevers, 2004, Kiecolt-Glaser and Glaser, 2002). The relationship between inflammation and depression is bidirectional (Kiecolt-Glaser *et al.*, 2015) and is more closely related to the physical symptoms of depression: tiredness, sleep problems and lack of appetite (Jokela *et al.*, 2015). Interventions that reduce inflammation markers include cognitive-behavioural therapy, exercise and meditation, and selective serotonin reuptake inhibitors (SSRIs) (Irwin and Cole, 2011, Vogelzangs *et al.*, 2012).

Second, hyperactivity of the hypothalamic pituitary adrenal (HPA) axis is observed in 50% of depressed individuals, and in 80% of those severely depressed (Anacker *et al.*, 2011). The feedback regulation of the axis is impaired, likely due to the abnormal function of the glucocorticoid receptors (Anacker *et al.*, 2011). As a result of the malfunction of this axis, hypercortisolemia in the blood is associated with insulin resistance, accumulation of intra-abdominal fat and lowered bone density (Cuijpers and Schoevers, 2004). The causal relationship between abnormalities of the HPA axis and depression has been unclear, and it has been suggested that both are caused by another factor, such as stress or trauma (Cuijpers and Schoevers, 2004). However, increasing evidence suggests that malfunction of the HPA axis may play a causal role in the development of depression: for example, polymorphisms of the glucocorticoid receptors have been associated with increased incidence of affective disorders (Cuijpers and Schoevers, 2004). Glucocorticoid treatment sometimes induces depressive symptoms, and elevated glucocorticoid levels result may reduce hippocampal neurogenesis (Anacker *et al.*, 2011). Differences between subtypes of depression have been documented, showing that persons with atypical depression might suffer from hypocortisolism, as opposed to the hypercortisolism seen in melancholic depression (Gold, 2015).

Third, depression is associated with increased noradrenaline levels. The sympathoadrenergic dysregulation and autonomic hyperactivity can lead to reduced heart rate variability and increased risk of cardiovascular events (Cuijpers and Schoevers, 2004).

### **2.6.5.5 Antidepressants**

Concerns exist regarding the impact of antidepressants on mortality, and, in particular, the tricyclic antidepressants that have potentially dangerous side effects, including cardiac conduction abnormalities (Somberg and Arora, 2008). At the population level, mortality among antidepressant users is higher compared to non-users, and increases further with use of other psychotropic medications (Palmaro *et al.*, 2015, Sundell *et al.*, 2011). However, in these register-based studies, users and non-users have different rates of depression, which makes interpretation of the results difficult.

Among people with a previous suicide attempt, the use of selective serotonin reuptake inhibitors (SSRI) is associated with decreased all-cause mortality (RR 0.59) because of lower risk of cardiovascular and cerebrovascular deaths (Tiihonen *et al.*, 2006). On the other hand, among elderly depressed persons, antidepressant users had a 1.7-fold mortality risk compared with non-users (Coupland *et al.*, 2011). Again, in this naturalistic study, use of antidepressants could be an indicator of disorder severity, and the mortality risk could be attributable to the disorder itself. In summary, methodological challenges limit the conclusions that can be made regarding the impact of antidepressants on mortality.

### **2.6.5.6 Health care utilisation**

Even though people with depression have higher prevalence of many chronic somatic conditions, they do not always receive adequate treatment for these conditions (Fagiolini and Goracci, 2009, Lawrence and Kisely, 2010). People with psychiatric disorders have fewer medical visits than the general population (Cradock-O'Leary *et al.*, 2002), and their use of primary care and preventive services is particularly low (Salsberry *et al.*, 2005). People with mental problems report more problems accessing general medical care than psychiatric care (Zeber *et al.*, 2009). Reasons for not seeking help are related to lack of recognition of symptoms and the reluctance to seek care, lack of social support and isolation, and the cost of care, especially in settings where access to health care is associated with employment (Fagiolini and Goracci, 2009, Zeber *et al.*, 2009).

The care received may be of worse quality than that provided to the general population. For example, patients with mental disorders and diabetes were less likely to receive appropriate laboratory and eye exams, and were more likely to be in poor glycaemic control than people without mental health problems (Frayne *et al.*, 2005). People with mental illness are also less likely to receive invasive coronary interventions, and have increased cardiac mortality following cardiac events (Kisely *et al.*, 2007, Mitchell and Lawrence, 2011).

The inequities in medical care received by people with mental disorders occur partly due to lack of information and communication problems with general healthcare workers, who might misattribute physical symptoms to mental disorder (Fagiolini and Goracci, 2009). Negative stereotypes may also lead to treating people with mental disorders less thoroughly (Thornicroft, 2011).

Finally, depressed persons are three times more likely to be nonadherent to their medication (DiMatteo *et al.*, 2000). Three possible explanations for this are: 1) depressed persons are so hopeless that they do not develop positive expectations of the treatment, which would be important to achieve treatment adherence; 2) social isolation and the lack of family support that often follow from depression may negatively influence adherence; 3) problems in cognitive functioning and memory impairment in particular might be obstacles to adhering to treatment.

## **2.7 SUMMARY OF THE LITERATURE REVIEW AND GAPS IN KNOWLEDGE**

While some issues regarding the prevalence, risk factors, prognosis and mortality in depressive disorders are relatively well-established and documented, the evidence is contradictory regarding others, and in some cases, there are apparent gaps in knowledge.

Although it is clear that the annual prevalence of major depressive disorder is approximately 5% with wide global variations, it is not known to what extent non-participation in surveys influences prevalence estimates. There is little reliable and recent information on the prevalence of dysthymia, another important contributor to the burden of mental illness. It is also unclear whether there have been changes in prevalence rates in the past decade, as most studies on prevalence changes compare 1990s with the 2000s, or even earlier time points.

Established risk factors of new-onset depressive disorders include female gender, childhood adversities (although this may be influenced by memory bias), chronic somatic conditions and other psychiatric disorders. The findings are inconsistent regarding the impact of marital and socioeconomic status, and very limited regarding social capital.

Prognosis of MDD in population surveys appears rather good, with three quarters experiencing recovery. Less is known about the prognosis of dysthymia. Some factors – single marital status and disorder severity – have been consistently associated with worse outcomes, but results are mixed regarding the impact of age, gender, socioeconomic position and other

factors. The broader spectrum of outcomes, including consequences involving self-rated health, health-related quality of life and residual symptoms, is less well documented than remission and recovery.

Finally, while the mortality risk in depressive disorders is estimated to be twofold, more recent and better studies report lower estimates. It is unclear whether the mortality risk has been exaggerated by poor-quality studies, and whether the risk differs by gender. Much less is known about excess mortality in anxiety and alcohol use disorders, even though both disorder groups are major public health concerns.



### **3 AIMS OF THE STUDY**

The overall aim of this study was to examine prevalence, predictors and different adverse outcomes of depressive disorders in a general population setting.

The specific aims were to:

1. Establish the prevalence of depressive disorders (MDD and dysthymia) in the Finnish population in 2011, and assess possible changes in prevalence from year 2000 to year 2011 (Sub-study I)
2. Examine risk factors for new-onset depressive disorders in an 11-year follow-up (Sub-study II)
3. Investigate the long-term prognosis of depressive disorders in a population sample using various outcome measures, and examine different predictors of adverse outcomes (Sub-study III)
4. Assess excess mortality associated with depressive, anxiety and alcohol use disorders and psychological distress and depressive symptoms, and describe the principal causes of death in a general population (Sub-study IV)

## **4 MATERIALS AND METHODS**

### **4.1 DATA SOURCES**

Data from the following sources were used in the study: the Health 2000 and Health 2011 population health surveys; the Finnish Care Register for Health Care; the Finnish Causes of Death Statistics held by Statistics Finland.

#### **4.1.1 HEALTH 2000 SURVEY**

The Health 2000 Survey is a nationally representative survey of the Finnish population (Heistaro, 2008). It was conducted in 2000-2001. A total of 8,028 adults aged 30 years and over (the adult sample) were sampled using stratified two-staged cluster sampling. The sample frame was the population-wide insurance database held at the Social Insurance Institution (Kela). In the first stage, 80 health centre districts (clusters) out of a total of 249 were sampled, 16 from each of the five main hospital districts of Finland. Out of these 80 clusters, 15 represented the largest cities in Finland, and the remaining 65 were sampled using systematic probabilities proportional to size design. In the second stage, individuals from these 80 clusters were sampled by systematic random sampling. Persons aged 80 and over were oversampled (2:1). In addition, a sample of young adults aged 18-29 (n=1894) took part in the survey of young adults, which had a shortened version of the study protocol (Figure 1, Table 6).

The adult sample study protocol consisted of a home interview, self-administered questionnaires and a health examination. In total, 7419 persons (93%) participated in at least some part of the study.

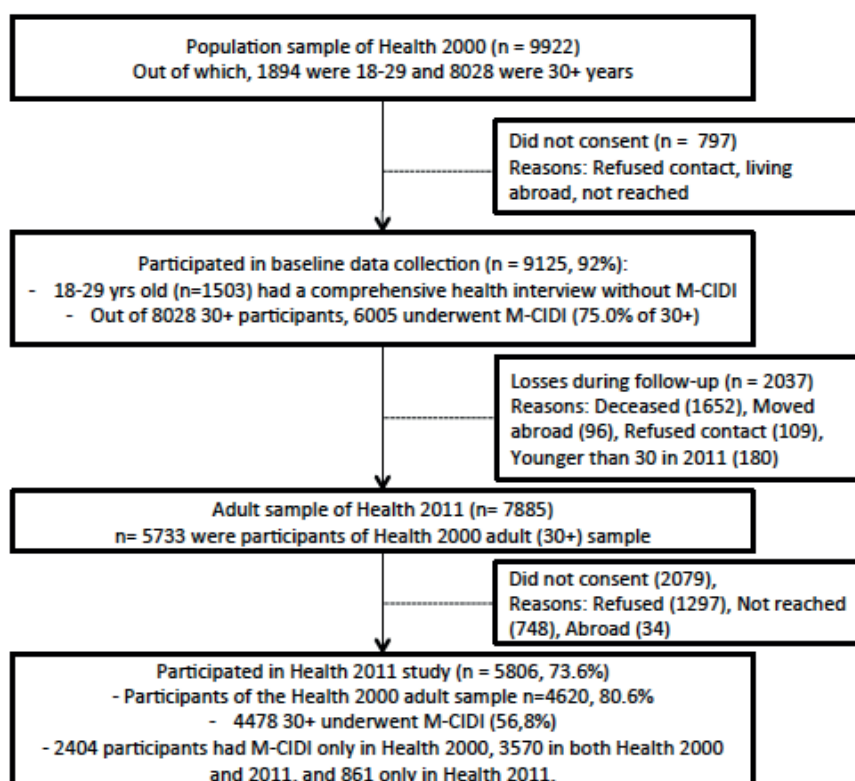
The study had the approval of the Ethics Committee of the Hospital District of Helsinki and Uusimaa. Written informed consent was obtained from the participants.

#### **4.1.2 HEALTH 2011 SURVEY**

The Health 2011 Survey is a follow-up study of the Health 2000 (Koskinen, 2012). The whole sample of the Health 2000 Survey, consisting of people who were alive, living in Finland, and had not refused to participate, were invited to take part. The young adults sample from Health 2000, of people who were 29-40 years of age in 2011, was included. In addition, there was a new young adults sample (18-29 years) in the survey, but this was not

included in the current study. Data were collected between August 2011 and June 2012.

The adult sample study population was 7,885 individuals, of whom 5,806 (74%) individuals participated in at least one part of the study (Figure 1, Table 6). The study had the approval of the Ethics Committee of the Hospital District of Helsinki and Uusimaa. Participants provided written informed consent.



**Figure 1** Participation and non-participation in the Health 2000 and Health 2011 Surveys

**Table 6.** Study population and register data used in the four sub-studies

	Health 2000	Health 2011	Register data
Sub-study I	30 years and over, n=8028	30 years and over, n=7885	Care Register for Health Care (multiple imputation)
Sub-study II	30-65 years without current or past depressive disorder, n=4057	41 years and over, n=3862	Care Register for Health Care (multiple imputation)
Sub-study III	30 years and over with 12-month depressive disorder, n=392	41 years and over, n=5733	Care Register for Health Care (multiple imputation), Finnish Causes of Death Statistics (vital status)
Sub-study IV	30 years and over, n=8028	-	Finnish Causes of Death Statistics (vital status and cause of death)

### 4.1.3 REGISTER DATA

#### 4.1.3.1 Care Register for Health Care (HILMO)

The Finnish Care Register for Health Care, a continuation of the Hospital Discharge Register, is managed by the National Institute for Health and Welfare. It covers all hospitalisations in public and private hospitals in Finland. Since information on specialised outpatient care was available only since 1994, it was not utilised in this study. In this study, Sub-studies I-III used information from the HILMO register for multiple imputation. Information on lifetime psychiatric hospitalisations of both participants and non-participants of the Health 2000 sample was obtained from the register and used in the studies as presented in Table 7. Information was available from 1969 onwards. Lifetime instead of past-year hospitalisations were used because of the low number of past-year hospitalisations.

**Table 7.** Care Register for Health Care information used in Sub-studies I-III.

Variable	Details	Sub-study I	Sub-study II*	Sub-Study III
Any psychiatric disorder by 2000	Hospitalisations for any psychiatric disorder (F04-F99; ICD-8 and ICD-9: 291-319) during 1969-2000	X		X
Schizophrenia by 2000	Hospitalisations for schizophrenia (ICD-10: F20; ICD-8 and ICD-9: 295.0-295.3, 295.5, 295.6, 295.8, 295.9) during 1969-2000	X		X
Non-affective psychoses by 2000	Hospitalisations for non-affective psychoses (ICD-10: F22, F23, F24, F25, F28, F29; ICD-8 and ICD-9: 295.4, 295.7, 297, 298, 299) during 1969-2000	X		X
Depressive disorders by 2000	Hospitalisations for depressive disorders (ICD-10: F32, F33, F341; ICD-9 (1987-1995) 2961, 3004A; ICD-8: 2960, 2962) during 1969-2000	X		X
Anxiety disorders by 2000	Hospitalisations for anxiety disorders (ICD-10: F40, F41, F42, F430, F431; ICD-9 and ICD-8: 3000, 3002, 3003) during 1969-2000	X		
Alcohol use disorders by 2000	Hospitalisations for alcohol use disorders (ICD-10: F10; ICD-9: 303, 3050, 291; ICD-8: 303, 291) during 1969-2000	X		X
Dementia by 2000	Hospitalisations for dementia (ICD-10: F00-F03; ICD-9 and ICD-8 290) during 1969-2000	X		X
Any psychiatric disorder by 2011	Hospitalisations for any psychiatric disorder (F04-F99; ICD-8 and ICD-9: 291-319) during 1969-2011	X	X	
Schizophrenia by 2011	Hospitalisations for schizophrenia (ICD-10: F20; ICD-8 and ICD-9: 295.0-295.3, 295.5, 295.6, 295.8, 295.9) during 1969-2011	X		X
Non-affective psychoses by 2011	Hospitalisations for non-affective psychoses (ICD-10: F22, F23, F24, F25, F28, F29; ICD-8 and ICD-9: 295.4, 295.7, 297, 298, 299) during 1969-2011	X		X
Depressive disorders by 2011	Hospitalisations for depressive disorders (ICD-10: F32, F33, F341; ICD-9 (1987-1995) 2961, 3004A; ICD-8: 2960, 2962) during 1969-2011	X	X	X
Anxiety disorders by 2011	Hospitalisations for anxiety disorders (ICD-10: F40, F41, F42, F430, F431; ICD-9 and ICD-8: 3000, 3002, 3003) during 1969-2011	X		X
Alcohol use disorders by 2011	Hospitalisations for alcohol use disorders (ICD-10: F10; ICD-9: 303, 3050, 291; ICD-8: 303, 291) during 1969-2011	X		X
Dementia by 2011	Hospitalisations for dementia (ICD-10: F00-F03;x ICD-9 and ICD-8 290) during 1969-2011	X		X

\*In Sub-Study II persons with hospitalisations due to depressive disorders prior to 2000 were excluded from the analyses and only hospitalisations between 2000-2011 were utilised in MI

#### **4.1.3.2 Mortality register (Sub-studies III-IV)**

Mortality data, including dates and causes of death, was obtained from the Causes of Death register from Statistics Finland (Finland, 2014). The data are compiled from death certificates, which are completed by the treating physician, or in the case of an unexpected or unnatural death, a medico-legal officer based on a forensic autopsy. This is the case in 25-30% of deaths, which is why Finnish mortality statistics are considered very reliable (Ylijoki-Sorensen *et al.*, 2014).

## **4.2 THE CIDI INTERVIEW**

Psychiatric disorders in the Health 2000 and Health 2011 surveys were diagnosed with the Composite International Diagnostic Interview, Munich version (M-CIDI) (Wittchen and Pfister, 1997). When designing the Health 2000 Survey, this was considered the best computerised version of the CIDI available. The Munich version was based on CIDI 2.1, the latest version at the time.

The predecessor of CIDI is the Diagnostic Interview Schedule (DIS), the first fully structured psychiatric diagnostic interview that could be administered by trained lay interviewers (Andrews and Peters, 1998, Kessler and Ustun, 2004). The CIDI was developed by an international task force, supported by the WHO and led by Dr. Robbins, the developer of the DIS. It was created in response to a need for reliable psychiatric instruments based on ICD criteria that could be used in population surveys to allow international comparison. The CIDI became available in 1990 and was used in several large population studies in its first years. The International Consortium in Psychiatric Epidemiology (ICPE) was created by the WHO to compare the results. To improve comparability of not only diagnoses, but also of risk factors, access to treatment and other important aspects of mental illness, the ICPE formed the WHO World Mental Health Survey Initiative and developed an improved and expanded version of the CIDI, the WMH-CIDI. The new version included modules covering functioning, treatment, risk factors, socio-demographic correlates and methodological issues, in addition to psychiatric diagnoses (Kessler and Ustun, 2004).

The Munich version of the CIDI (M-CIDI) was developed parallel to CIDI 2.1, as there was a need to update the interview to correspond to DSM-IV diagnostic criteria, as well as some technical revisions. The development was done in collaboration with the WHO-CIDI consortium, and the M-CIDI corresponds closely to the WMH-CIDI. The M-CIDI has shown good test-retest reliability ( $\kappa$  values 0.68 for major depressive disorder and 0.70 for dysthymia) in a sample of 60 persons aged 14-28 years, with a mean interval between interviews of 39 days (Wittchen *et al.*, 1998).

The different versions of the CIDI are commonly used in general population mental health surveys (Kessler and Ustun, 2004), and international comparability is its major strength. It has shown good concordance with more thorough semistructured psychiatric interviews, such as the Structured Clinical Interview for DSM (SCID) (Andrews and Peters, 1998, Haro *et al.*, 2006). In an international validity study of the CIDI 3.0 (Haro *et al.*, 2006), the sensitivity for any 12-month mood disorder was 69.1 and specificity was 97.2, positive predictive value 49.6 and negative predictive value 98.7, with the SCID as comparison. In the National Comorbidity Survey (NCS-R), validity of the Major Depressive Episode module of the CIDI was assessed, with sensitivity of 54.6, specificity 94.7, total classification accuracy 90.7, positive predictive value 64.1 and negative predictive value 97.5 (Kessler *et al.*, 2003).

The M-CIDI has been compared to clinician diagnoses with excellent results: the sensitivity and specificity of the depression module were 95 and 100 for lifetime single and 93 and 100 for recurrent depressive episode, and 100 and 85 for dysthymia, respectively, with corresponding Kappa values 0.96, 0.95 and 0.54 (Reed *et al.*, 1998). The lower Kappa value for dysthymia was due the M-CIDI not applying an optional hierarchy rule where a history of long unremitted MDD outweighs diagnosis of dysthymia.

However, in the case of population studies, it can be argued that, in addition to individual-level concordance, a measure of aggregate-level concordance (i.e. agreement of prevalence rates of two different instruments) is important (Kessler *et al.*, 2004). In the case of CIDI 3.0, there was no statistically significant difference between the 12-month prevalence rates produced by SCID or CIDI interviews, whereas lifetime prevalence of MDD was 33% higher when using SCID (Haro *et al.*, 2006).

The full M-CIDI interview lasts about 90 minutes, and had to be cut down for the Health 2000, as it was part of a more extensive general health survey. In 2000, six sections were included: anxiety disorders, depressive disorders, mania, schizophrenia and other psychotic disorders, alcohol use disorders and other substance-related disorders. In addition, interviewer observations were recorded. In 2011, sections on mania and other substance-related disorders were not included, and the section on psychotic disorders was shortened. Altogether eight disorders were covered in both in 2000 and 2011: panic disorder, agoraphobia, social phobia, generalised anxiety disorder, dysthymia, major depressive disorder, and alcohol abuse and dependence. Only 12-month prevalence was determined, except for alcohol use disorders, for which also lifetime prevalence was assessed. Diagnostic criteria of the DSM-IV were used.

The M-CIDI was translated from its English version into Finnish for the Health 2000 and pilot-tested. Test-retest reliability was assessed for the depression and dysthymia modules, and the inter-rater agreement was excellent with  $\kappa$  values 0.88 for both disorders and percentage of agreement 94-98% (Heistaro, 2008).

In Health 2011, the time available for the mental health interview was reduced further, and modules had to be prioritised based on their public health importance and experience from Health 2000. The sections assessing manic symptoms and substance use other than alcohol were omitted. The translation from Health 2000 was revised against the original German version and the English translation. The new CIDI was piloted and all errors were corrected before beginning the study. The interviewers, non-psychiatric health professionals, received a two-day training. The interview was carried out at the end of the health examination or, in some cases, during the home interview. The mean duration was 21 minutes, ranging from 2.6 to 176 minutes.

In 2000, a total of 6,005 CIDI interviews (75% of the sample) were conducted and in 2011, the total was 4,478 (57%). Altogether 3,584 people were interviewed both in 2000 and 2011.

The Psychoses in Finland study was carried out parallel to the Health 2000 Survey to identify persons with psychotic disorders (Perälä *et al.*, 2007). Psychotic disorders were screened using the Composite International Diagnostic Interview, self-reported diagnoses, medical examination, and national registers on hospitalisations, medication and disability pensions. Lifetime diagnosis of psychotic disorders was established with the Research Version of the Structured Clinical Interview for DSM (SCID) and a review of medical records (First, 1997). In this study, people with a psychotic disorder were excluded from Sub-study II, and the results of Sub-studies III and IV were adjusted for psychotic disorders. In Sub-study III, the impact of comorbid psychotic disorder on the prognosis of depressive disorder was studied.

## **4.3 STUDY VARIABLES**

### **4.3.1 OUTCOME VARIABLES**

#### **4.3.1.1 Diagnostic status at follow-up (Sub-studies I-III)**

The presence of depressive disorders in 2011, MDD and dysthymia, was used as the primary outcome measure in sub-studies I-III. For both studies, these



were combined as a group, depressive disorders, containing people with MDD, dysthymia or both.

Also, the presence of any depressive, anxiety or alcohol use disorder was considered as an outcome in Sub-study III.

#### **4.3.1.2 New-onset depression (Sub-study II)**

To analyse risk factors for incident or new-onset cases of depressive disorders only, people with a history of depressive disorder at baseline were excluded to the extent possible. People were excluded who in the Health 2000 survey had received a 12-month diagnosis of MDD or dysthymia in the CIDI interview, had ever been hospitalised for a depressive disorder, or reported having received a depression diagnosis from a physician. People with any psychotic disorder in 2000 were also excluded, as they were considered to likely differ from the general population in terms of risk factors for onset of depression.

#### **4.3.1.3 Recovery and persistence (Sub-study III)**

Recovery was defined as not meeting diagnostic criteria for either MDD or dysthymia in the past 12 months. This is consistent with the definition of recovery presented by Frank et al. (Frank *et al.*, 1991) where recovery is defined as having no symptoms or minimal symptoms for 4-6 months. We did not, however, take into account residual symptoms measured with the BDI, to allow comparison to other similar studies.

Persistence of disorder was defined as having a depressive disorder both at baseline and follow-up. Since there was no information on the health status between these two timepoints, it could not be established whether this was a chronic, ongoing episode or a recurrent episode. The term “persistence” was chosen to reflect both options.

#### **4.3.1.4 Depressive symptoms and psychological distress (Sub-study III)**

The Beck Depression Inventory (BDI) was used to assess current depressive symptoms both at baseline and at follow-up (Beck *et al.*, 1961). The 21-item version was used in 2000, and a shorter 13-item version, validated by Aalto et al., was used in 2011 (Aalto *et al.*, 2012). The total score was divided into three categories, indicating no significant depressive symptoms, moderate, and severe depressive symptoms as follows: 0-9, 10-18 and 19 points or more in 2000, and 0-4, 5-8 and 9 or more points in 2011.

Current psychological distress was measured using the General Health Questionnaire (GHQ), where a score of 4 or more indicated psychological distress (Goldberg *et al.*, 1997).

It is noteworthy that the CIDI diagnoses covered the 12 months preceding the study, meaning that some persons had already recovered by the time of the interview. In contrast, the BDI and GHQ measured current symptoms. Both were part of a larger self-administered questionnaire sent to the participants to be completed prior to the physical health exam.

#### **4.3.1.5 Health-related quality of life (Sub-study III)**

Health related-quality of life at follow-up was measured with the EQ-5D instrument, which was converted into an index score based on time-trade-off values elicited in a UK general population sample (Kind *et al.*, 1999).

#### **4.3.1.6 Self-rated health (Sub-study III)**

Self-rated health at follow-up was measured by asking the respondents to assess their current health status by rating it as good, rather good, moderate, rather poor or poor.

#### **4.3.1.7 Mortality and causes of death (Sub-studies III-IV)**

Mortality data was obtained from the Statistics Finland Causes of Death Register, as described above. In Sub-study III, only information on vital status at the beginning of Health 2011 data collection (4 July 2011) was used.

In Sub-study IV, date and cause of death were included in the analyses. The causes of death were categorised into natural deaths (ICD-10 codes A00-R99), suicides (X60- X84), homicides (X85-Y09) and other unnatural deaths, such as accidents, injuries and poisonings (S00-T98, V01-X49 and Y40-Y98). The natural causes of death were further categorised into four classes: tumours (C00-D48), cardiovascular diseases (I00-I99), pulmonary diseases (J00-J99), and other (A00-B49, D50-H95, K00-N99, O00-R99).

### **4.3.2 EXPOSURE AND CONFOUNDER VARIABLES AT BASELINE**

#### **4.3.2.1 Sociodemographic variables (all Sub-studies)**

Sociodemographic information was obtained in a structured interview. Educational level, based on the highest level completed, was divided into

three categories: basic (no high school or vocational training); secondary (high school or completed vocational school); and higher (degree from a higher vocational institution, polytechnic or university). Marital status was categorised into married and cohabiting; and single, which included those never-married, divorced or widowed. Family income was obtained from registers of the Finnish Tax Administration, adjusted for family size, and divided into quintiles.

#### **4.3.2.2 Childhood adversity (Sub-studies II-III)**

Childhood adversities were elicited using an 11-item questionnaire “When you think about your growth years, i.e. before you were aged 16, did you...?”, with answer options “yes”, “no” or “cannot say” (Pirkola *et al.*, 2005a). The items inquired were

1. Did your family have long-term financial difficulties?
2. Were your father or mother often unemployed although they wanted to work?
3. Did your father or mother suffer from some serious disease or disability?
4. Did your father have alcohol problems?
5. Did your mother have alcohol problems?
6. Did your father have any mental health problem, e.g., schizophrenia, other psychosis, or depression?
7. Did your mother have any mental health problem, e.g., schizophrenia, other psychosis, or depression?
8. Were there any serious conflicts within your family?
9. Did your parents divorce?
10. Were you yourself seriously or chronically ill?
11. Were you bullied at school?

The total number of reported adversities was counted and categorised into 0, 1-2 and 3 or more reported adversities, as in Kananen *et al.* (2010). In sub-study II, parental mental health problems (items 6 and 7) were included in the models separately, and not included in the summary variable. In sub-study III, they were first explored separately in the unadjusted logistic models, and then included in the summary variable in the adjusted logistic models.

#### **4.3.2.3 Social capital (Sub-studies II-III)**

Social capital was conceptualised as a three-dimensional measure, assessing social support, social participation and trust, based on the work by Nieminen *et al.* (Nieminen *et al.*, 2008). These dimensions concur with those proposed

by a broad international consensus (Zukewich and Norris, 2005). The indicator was created using factor analysis to divide 39 variables into the three chosen dimensions. The items included in the three dimensions are listed in Table 8.

The dimension of trust included questions about feeling safe in the neighbourhood, disappointments caused by people close to you, and cynical mistrust, which was measured on an eight-item scale, shortened from the Cook-Medley hostility scale (Nieminen *et al.*, 2008).

**Table 8.** *Items in the three dimensions of the social capital measure (adapted from Nieminen et al. (2008))*

Social support	Social networks and participation	Trust
People on whose help you can count when you feel exhausted	Club and society activities	Feeling safe in neighbourhood
People you think really care about you no matter what	Theatres, movies	Feeling safe walking out alone after 10 p.m.
People that can really make you feel better when you feel down	Studying	Cynical mistrust (8 questions)
People from whom you get practical help when needed	Church and religious activities	Been surprised by the behaviour of people you thought you knew well
	Exercise, fishing, gardening etc. outdoor activities	People you counted on disappointed you
	Handicrafts, playing music, singing	
	Visiting family, friends or neighbors	
	Having family, friends or neighbours visit you	
	Talking on the phone	
	Joining in any health promotion/discussion group (11 questions about health promotion)	

#### 4.3.2.4 Somatic comorbidity, smoking and obesity (Sub-studies II-IV)

Somatic comorbidity was assessed based on self-reported diseases that had been diagnosed by a physician. At baseline, participants were asked whether they had received diagnosis from a doctor for 43 different conditions, and in some cases, to provide details on treatment and intensity of the condition. For this study, 24 conditions were chosen based on relevance to mortality and comorbidity, and the reliability of self-report (Saarni *et al.*, 2006). These were categorised into eight groups: cardiovascular diseases (heart failure,

myocardial infarction, coronary heart disease, hypertension and stroke); pulmonary diseases (chronic obstructive pulmonary disease, chronic bronchitis and asthma); neurological diseases (migraine, Parkinson's disease); musculoskeletal disorders (rheumatoid arthritis, osteoarthritis, back or neck disease requiring a visit to a physician in the past 12 months); vision and hearing disorders (unoperated cataract, glaucoma, macular degeneration, hearing loss, tinnitus), and other diseases (disturbing allergy requiring a visit to a physician in the last 12 months, psoriasis, inflammatory bowel disease and urinary incontinence). Cancer and diabetes were included separately. In Sub-studies II-III, somatic comorbidity was categorised into 0, 1-2 and 3 or diseases, whereas in Sub-study IV, the eight categories were included as such.

Participants were classified into three categories based on smoking status: current smokers (smoked at least 100 times in their lifetime, smoked regularly for the past year, and most recently during the past month), ex-smokers, and non-smokers.

Body-mass index (BMI) was calculated based on height and weight measurements at the health examination.

## **4.4 STATISTICAL METHODS**

In all sub-studies, sociodemographic and other baseline characteristics were compared among different subgroups using the chi-square test for categorical and t-test for continuous variables. All tests were two-tailed, and p-value of  $<0.05$  was chosen to denote statistical significance. The stratified two-stage cluster sampling was accounted for by using survey procedures of the statistical software. Weights were used to adjust for the oversampling of individuals aged 80 and over, where the analytic sample was not limited to younger individuals.

The R statistical software (version 3.1 for Linux) was used to carry out multiple imputation. Other analyses, including analysis of the imputed data in Sub-studies I-III, were done using the Stata statistical software package (version 11.2 for Windows).

### **4.4.1 MULTIPLE IMPUTATION**

Participation in the Health 2011 was much lower than in Health 2000, at 73% vs. 93%, and participation in the CIDI, in particular, was low, at 75% vs. 57%. From previous studies, it was known that attrition is selective, and persons with mental disorders have a lower likelihood of participating.

Therefore, this non-participation needed to be accounted for. Two methods were compared: inverse probability weights (IPW) and multiple imputation (MI). IPW are technically easier to apply and are more frequently used, but the MI is more efficient and flexible (Härkänen *et al.*, 2016, Li *et al.*, 2015, Mackinnon, 2010, Rubin, 1978).

Multiple imputation replaces the missing values by numbers based on associations among the observed values in the data set (Li *et al.*, 2015). This process of generating the replacement values is repeated many times, producing several copies of the original data sets, but with no missing values. Then, the imputed data sets are analysed separately according to the desired statistical analysis, such as regression, and finally the results are combined into a single estimate. As opposed to other forms of imputation (such as means or single imputation), it does not create false precision in the data.

In this study, register data on hospitalisations for psychiatric disorders, as presented in Table 7, and information from the Health 2000 interview was utilised in the multiple imputation. In Sub-study I, the criteria for including variables into the imputation model were that they had to have more than 5% points more observed values than the outcomes and a Pearson correlation higher than 0.20 with the outcomes. In Sub-studies II-III, the register variables with highest correlation, as well as all the variables from the regression models were included. The exact variables used for each of the Sub-studies I-III are reported in the Supplementary tables of the studies.

The MI was based on chained equations (ICE) (van Buuren and Groothuis-Oudshoorn, 2011) and regression trees (Therneau *et al.*, 2015) suitable for imputing categorical variables, such as the needed outcome variables: MDD and dysthymia diagnoses. In Sub-study I, both baseline and follow-up datasets were imputed simultaneously, by groups defined by age and gender. A total of 20 imputed data sets were constructed in Sub-study I; 24 in Sub-study III; and 35 in Sub-study II.

In Sub-Study I, the MI was based on the total sample of Health 2000 (a total of 8,028 people) whereas in Sub-Study II, it was based on the sample of 4,057 participants without depression at baseline, and in Sub-Study III, on the 7,112 people who participated in at least some part of the study. It was considered that imputing all the missing values would not have reflected true associations in the group of nonrespondents.

#### **4.4.2 WEIGHTS**

Multiple imputation was compared to the more traditional method of accounting for non-response, inverse probability weights, which were applied

in the Health 2011 Survey. Their purpose is to generalise the data to represent the survey's target population, and adjust for the effect of non-participation. Inverse probability weights were created using the participation probabilities estimated by a logistic regression model, which were then calibrated with respect to known population distributions, such as age and gender distributions. Sociodemographic information from Statistics Finland and data from the baseline survey were used for this purpose, whereas disease-specific information from the Care Register for Health Care was not used.

In the Health 2000 Survey, poststratification weights were applied. They were based on the design weights, which are simply the inverse of the inclusion probability of an individual. They were then calibrated using poststratification according to known population characteristics: health care district, university hospital district, age, gender and mother tongue (Heistaro, 2008).

Design weights to account for the oversampling of individuals aged 80 and over were also used in the MI analyses (Sub-studies I and III)

#### **4.4.3 SUB-STUDY I**

In Sub-study I, age and gender adjusted prevalences were estimated using the predictive margins method (Lee, 1981). Prevalences in 2000 and 2011 were compared by adjusting for changes in the population so that the standard population was chosen to be the 2011 population. This allowed for analysis of time trends taking into account the changes that had occurred in the age and gender distribution of the Finnish population. Logistic bivariate and multivariate regression was used to analyse associations between independent and dependent variables.

We used two methods to adjust for non-response: inverse probability weighting (IPW) and multiple imputation (MI).

#### **4.4.4 SUB-STUDY II**

Logistic bivariate and multivariate regression models were used to analyse risk factors of new-onset depression (MDD or dysthymia) in the working-aged population (30-65 years at baseline). Six regression models were built by subsequently adding new risk factors and confounders to those of the previous model: 1) age and sex; 2) education, income and marital status; 3) childhood adversities and paternal mental disorder; 4) social capital; 5) somatic diseases; 6) mental health (anxiety and alcohol use disorders,

baseline depressive symptoms). Separate multivariate regression models were built to analyse risk factors for MDD only and dysthymia only, where only models 1 and 6 were used. Multiple imputation was used to handle missing data.

#### **4.4.5 SUB-STUDY III**

In Sub-study III, prevalences with their corresponding confidence intervals were used to describe diagnostic status at follow-up in the baseline MDD and dysthymia groups. Proportions and means were used to describe depressive symptoms, psychological distress, quality of life and self-rated health at follow-up in the two groups. These were further stratified into those who had recovered (no depressive, anxiety or alcohol use disorder at follow-up) and those who had not.

Logistic multinomial regression models were built to analyse associations between the predictors and two outcomes: death and persistence of depressive disorder. This was done to account for the impact of right censoring, where participants with the most severe disorder possibly also have the highest mortality risk. In the multinomial regression, the two outcome categories were compared against the reference category “alive and without depressive disorder.”

Linear regression was used to analyse depressive symptoms at follow-up based on the BDI-13 score. Upon analysing the linear regression model, 12 possibly outlying individuals were found and the analyses were performed excluding them, which did not impact the results.

Multiple imputation was used to account for missing data.

#### **4.4.6 SUB-STUDY IV**

In Sub-study IV, analyses were limited to age group 30-70 years, as participation in the CIDI interview in the older age groups was low, which could have distorted the results. Cox’s proportional hazards regression model was used to examine the risk of all-cause mortality. Four regression models were built to examine the impact of different confounders: 1) adjusting only for psychiatric comorbidity; 2) adjusting for marital status, education and income; 3) adjusting for health and health behaviour; 4) combining all confounders from models 1-3. All models were stratified for age and sex.

The models were tested to verify the proportional hazards assumption. This did not hold for the variable describing history of cancer diagnosis (p-value



0.044), because the mortality risk of persons with diagnosed cancer was high at the beginning of the follow-up and then decreased to level of risk close to the cancer-free population. Therefore, cancer diagnosis was added to the models through stratification, not direct adjustment.

## 5 RESULTS

### 5.1 PREVALENCE OF DEPRESSIVE DISORDERS (SUB-STUDY I)

In 2011, the 12-month prevalence of MDD was 7.4% (95% CI 5.7-9.0); higher in women (10.0%, 95% CI 8.2-11.8) than men (4.4%, 95% CI 2.1-6.7); and higher in the 30-44 year age group (9.6%, 95% CI 7.1-12.1). The prevalence of dysthymia was 4.5% (95% CI 3.1- 5.9) in the general population, with no significant gender or age differences (Table 9).

In adjusted logistic regression, female gender (adjusted OR 2.3, 95% CI 1.58-3.44), younger age, and being single (adjusted OR 1.5, 95% CI 1.19-2.01) were associated with a higher prevalence of MDD. Education was not associated with prevalence of MDD (Table 10).

Correlates of dysthymia in the adjusted logistic regression were low education and being single (adjusted OR 2.5, 95% CI 1.55-3.95) (Table 10, Markkula et al., previously unpublished results).

The prevalence of MDD, adjusted for sociodemographic changes that occurred in the population, increased in women by 2% points and in men by 0.9% points. This was significant in women ( $p=0.049$ ), but not in men ( $p=0.777$ ) (Figure 3). The prevalence of dysthymia did not change significantly ( $p=0.426$  for total population). When combined, the prevalence of depressive disorders increased by 2.3% points in the total population, which was significant ( $p=0.014$ ). The increase was significant in women (2.9% points,  $p=0.018$ ), but not in men (1.6%,  $p=0.323$ ).

Non-participation was selective, so that non-participants had higher prevalence of lifetime hospitalisations for depressive disorders than CIDI participants (3.8% vs. 1.7%, respectively). The difference was more marked in the age groups 65-74 years (3.6% vs. 1.6%) and 75 years and older (4.6% vs. 1.4%). A total of 71% of persons with lifetime psychiatric hospitalisations and 72% with lifetime hospitalisations for depressive disorders did not participate in the CIDI interview. Therefore, it is understandable that the prevalence rates based on MI utilising register data were higher than prevalence rates based on weights only. A comparison is presented in Table 9. The increase was, on average, 2% points. The increasing trend in prevalence was similar when using weights: the increase in prevalence of MDD from 2000 (4.6%) to 2011 (5.3%) was not statistically significant ( $p=0.057$ ), but still observed.

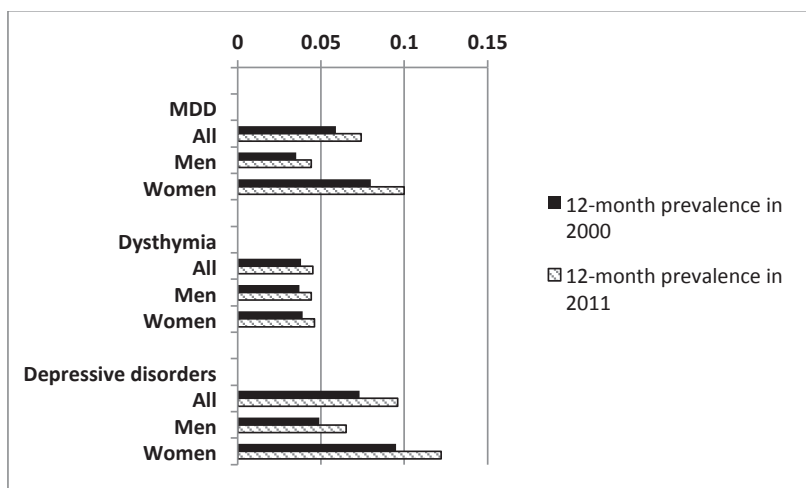
**Table 9.** 12-month prevalence of depressive disorders in Health 2011 by gender and age group, comparing multiple imputation (MI) and weights

	Prevalence with MI	95% CI with MI	Prevalence with weights	95% CI with weights
Depressive disorders	9.6	7.9-11.3	6.8	6.0-7.5
Women	12.2	10.1-14.3	8.4	7.3-9.6
Men	6.7	3.8- 9.6	4.9	3.9-5.9
Age 30-44 years	12.5	10.1-14.9	9.4	7.6-11.3
Age 45-54 years	12.0	9.7-14.2	8.9	7.1-10.6
Age 55-64 years	7.0	4.1- 9.8	6.5	5.1- 8.0
Age 65-74 years	5.8	3.4- 8.1	3.2	2.0- 4.5
Age 75 and over	8.0	1.1-14.9	1.9	0.6- 3.2
MDD	7.4	5.7- 9.0	5.4	4.7-6.1
Women	10.0	8.2-11.8	7.0	5.9-8.0
Men	4.4	2.1- 6.7	3.5	2.7-4.3
Age 30-44 years	9.6	7.1-12.1	7.8	6.1- 9.4
Age 45-54 years	9.2	7.2-11.2	6.9	5.3- 8.5
Age 55-64 years	5.1	3.3- 6.9	5.1	3.7- 6.4
Age 65-74 years	4.5	2.3- 6.6	2.6	1.5- 3.7
Age 75 and over	6.7	1.0-12.5	1.0	0.1- 1.9
Dysthymia	4.5	3.1- 5.9	2.0	1.6-2.4
Women	4.3	3.0- 5.7	2.2	1.6-2.9
Men	4.7	2.4- 7.0	1.7	1.1-2.4
Age 30-44 years	4.5	2.6- 6.4	2.8	1.7- 3.9
Age 45-54 years	4.3	2.7- 5.9	2.7	1.8- 3.7
Age 55-64 years	4.2	2.0- 6.5	1.8	1.0- 2.5
Age 65-74 years	4.0	1.9- 6.1	0.8	0.2- 1.5
Age 75 and over	6.3	0.5-12.0	0.9	0.0- 1.9

**Table 10.** Correlates of MDD and dysthymia in the Health 2011 Study

	MDD, adjusted OR (95% CI)*	Dysthymia, adjusted OR (95% CI)*
Men	1	1
Women	<b>2.33 (1.58-3.44)</b>	1.02 (0.62-1.70)
Age 30-44 years	1	1
Age 45-54 years	0.84 (0.63-1.13)	0.92 (0.55-1.54)
Age 55-64 years	<b>0.48 (0.34-0.70)</b>	0.65 (0.33-1.31)
Age 65-74 years	<b>0.29 (0.17-0.51)</b>	0.39 (1.14-1.02)
Age 75 years and over	<b>0.26 (0.07-0.91)</b>	0.49 (0.13-1.83)
Basic education	1	1
Intermediate education	0.78 (0.55-1.11)	<b>0.58 (0.34-0.99)</b>
High education	0.81 (0.57-1.17)	<b>0.48 (0.28-0.83)</b>
Married or cohabiting	1	1
Separated, widowed or unmarried	<b>1.54 (1.19-2.01)</b>	<b>2.47 (1.55-3.95)</b>

\*Adjusted for sex, age, educational level, marital status and region



**Figure 3** 12-month prevalence of depressive disorders in the Finnish population in 2000 and 2011

## 5.2 RISK FACTORS OF DEPRESSIVE DISORDERS (SUB-STUDY II)

At the follow-up, 104 new cases of MDD and 31 of dysthymia were diagnosed, 9 of who had both diagnoses. Incidence of depressive disorders differed between subgroups, being highest among persons with anxiety disorders (13.7%) and those with high BDI score (11.5%). In the complete sample, incidence of new-onset depression was 4.4% (95% CI 3.6-5.2%).

In the final adjusted logistic regression models, significant risk factors of new-onset depressive disorders were younger age, female gender, having three or more childhood adversities, low trust axis of social capital, anxiety disorder and depressive symptoms (Table 11). The predictors were different for the two depressive disorders. Risk factors for MDD were younger age (OR 0.97, 95% CI 0.95-0.99 per year), female gender (OR 1.68, 95% CI 1.11-2.55), anxiety disorder at baseline (OR 2.53, 95% CI 1.17-5.46) and subclinical depressive symptoms (OR 1.64, 95% CI 1.00-2.68 for moderate and OR 3.03, 95% CI 1.48-6.19 for severe depressive symptoms). Risk factors for dysthymia were younger age (OR 0.93, 95% CI 0.89-0.98 per year), three or more childhood adversities (OR 3.36, 95% CI 1.22-9.27), low trust axis of social capital (OR 0.30, 95% CI 0.09-0.97 for high trust) and chronic somatic diseases (OR 3.37 for 1-2 diseases, 95% CI 1.19-9.52).

**Table 11.** Incidence of depressive disorders by subgroup and adjusted odds ratio for new-onset depressive disorders in the Health 2011 Survey

	Incidence of depressive disorders (%)	P for difference	Adjusted OR for depressive disorders (95% CI)
<i>Sociodemographic characteristics</i>			
Age group: 30-44	5.4	0.033	0.97 (0.95-0.99)
Age group: 45-54	4.2		(per year)
Age group: 55-64	2.9		
Sex: male	3.5	0.018	1
Sex: female	5.3		1.46 (1.01-2.12)
Education: primary	3.6	0.420	1
Education: secondary	4.7		1.27 (0.75-2.15)
Education: tertiary	4.7		1.23 (0.73-2.09)
Income: 1 <sup>st</sup> quintile	4.3	0.974	1
Income: 2 <sup>nd</sup> quintile	4.8		1.23 (0.54-2.80)
Income: 3 <sup>rd</sup> quintile	4.0		0.99 (0.42-2.34)
Income: 4 <sup>th</sup> quintile	4.4		1.06 (0.46-2.47)
Income: 5 <sup>th</sup> quintile	4.5		1.17 (0.51-2.67)
Marital status: married	4.4	0.838	1
Marital status: unmarried	4.5		0.94 (0.56-1.61)
<i>Childhood adversities</i>			
No adversities	3.5	0.001	1
1-2	4.3		1.15 (0.78-1.70)
3 or more	7.6		1.76 (1.10-2.83)
Parental mental disorder	7.3	0.068	1.29 (0.66-2.53)
<i>Social capital</i>			
Axis 1: support low	4.1	0.825	1
Axis 1: support medium	4.4		1.06 (0.66-1.71)
Axis 1: support high	4.6		1.07 (0.66-1.73)
Axis 2: participation low	5.2	0.329	1
Axis 2: participation medium	3.7		0.66 (0.41-1.07)
Axis 2: participation high	4.5		0.74 (0.45-1.19)
Axis 3: trust low	6.0	0.006	1
Axis 3: trust medium	4.6		0.85 (0.55-1.30)
Axis 3: trust high	2.9		0.58 (0.36-0.96)
<i>Somatic morbidity</i>			
No somatic diseases	3.8	0.369	1
1-2 somatic diseases	4.8		1.32 (0.88-1.97)
3 or more somatic diseases	4.4		1.26 (0.60-2.90)
<i>Psychiatric morbidity</i>			
BDI 0-9	3.8	<0.001	1
BDI 10-18	6.7		1.65 (1.04-2.61)
BDI 19 or more	11.5		2.49 (1.20-5.17)
Anxiety disorder	13.7	<0.001	2.75 (1.36-5.56)
Alcohol use disorder	6.0	0.375	1.32 (0.60-2.90)

### 5.3 PROGNOSIS OF DEPRESSIVE DISORDERS (SUB-STUDY III)

A total of 392 people had a depressive disorder at baseline, out of whom 245 had MDD only, 94 dysthymia only and 53 both MDD and dysthymia. Of them, 40.2% had current severe depressive symptoms, measured with the BDI.

At the follow-up, 20.9% of people with baseline MDD and 27.0% of people with baseline dysthymia still had a depressive disorder, and 33.8% and 42.6% some depressive, anxiety or alcohol use disorder, respectively. Depressive symptoms were more common than diagnosis of depressive disorder: 47.6% of those with baseline MDD and 61.2% of those with baseline dysthymia still had significant depressive symptoms after eleven years (BDI-13 5 points or higher) (Table 12).

**Table 12.** *Diagnostic status and depressive disorders after eleven years follow-up by baseline diagnosis of depressive disorder (MDD or dysthymia)*

Diagnosis at baseline	No diagnosis in 2011 %	Any depressive, anxiety or alcohol use disorder in 2011 %	MDD in 2011 %	Dysthymia in 2011 %	Any depressive disorder %	BDI-13 score 5 or more %
<b>MDD in 2000 (n=298)</b>	66.2	33.8	16.0	8.1	20.9	46.5
<b>Dysthymia in 2000 (n=147)</b>	57.4	42.6	16.4	13.4	27.0	61.1

Also health-related quality of life, measured as the EQ-5D score, was lower than in the general population (Table 13). However, when separated by diagnostic status at follow-up, those who had recovered from MDD had values close to the general population, whereas those recovered from dysthymia still had lower quality of life and more depressive symptoms.

Also poor or rather poor self-rated health was more common than in the general population: 16.7% of persons with baseline MDD and 28.6% of persons with baseline dysthymia rated their health as poor or rather poor, compared with 10.8% of the total sample.

**Table 13.** *Depressive symptoms, quality of life and self-rated health of persons with MDD and dysthymia after eleven years follow-up*

	All	Baseline MDD		Baseline dysthymia	
		Recovered (no CIDI diagnosis in 2011)	Any CIDI diagnosis in 2011	Recovered (no CIDI diagnosis in 2011)	Any CIDI diagnosis in 2011
<b>No significant depressive symptoms (BDI-13 score 0-4) %</b>	75.4	65.4	27.3	53.3	18.0
<b>Moderate depressive symptoms (BDI-13 score 5-8) %</b>	12.0	16.2	15.7	24.7	12.4
<b>Severe depressive symptoms (BDI-13 score 9-39) %</b>	12.5	18.4	57.1	22.0	69.6
<b>Quality of life, EQ-5D (UK index, mean)</b>	0.81	0.80	0.72	0.73	0.65
<b>Self-rated health rather poor or poor %</b>	10.8	11.6	26.6	22.5	37.3

Single marital status (adjusted OR 1.91, 95% CI 1.05-3.56) and symptom severity at baseline (adjusted OR 1.05, 95% CI 1.01-1.09 per one point increase in BDI) were associated with persistence of disorder. Symptom severity at baseline also predicted more depressive symptoms at follow-up. No other studied factors, such as age, gender, education, history of childhood adversity, social capital, somatic or psychiatric comorbidity, were statistically significant predictors of outcomes of depression.

A total of 29 individuals with baseline MDD and 25 individuals with baseline dysthymia died during the follow-up. Older age, male sex and symptom severity as measured with the BDI were associated with higher mortality risk.

The analyses were also carried out using weights to account for non-participation, instead of MI. There were no important differences, but in the weighted models, also childhood adversity and low social capital were statistically significant predictors of poor outcomes of depressive disorders. All in all, the estimates were similar in direction and magnitude.

## **5.4 EXCESS MORTALITY IN DEPRESSIVE, ANXIETY AND ALCOHOL USE DISORDERS (SUB-STUDY IV)**

Altogether 323 deaths were observed over the eight-year follow-up period in the studied age group of 30-70-year-olds. Majority of deaths (82.9%) were natural, 11.7% were accidents, 5.1% (n=16) suicides, one homicide and one unknown. Of the 16 persons who committed suicide, five (38.5%) did not have a known psychiatric diagnosis, but many of them had more than one, the most common being MDD (5 persons), social phobia (5) and alcohol dependence (3).

Depressive disorders were associated with an increased mortality risk (fully adjusted HR 1.97, 95% CI 1.15-3.39) (Table 14). The unadjusted HR was 2.4, and was more affected by adjustment to sociodemographic factors (HR 1.7) than for health status and smoking (HR 2.2).

Among persons with anxiety disorders, a large share (50%) of deaths were unnatural, and in some disorders this figure was 80-100%. The mortality risk was increased (HR 2.32, 95% CI 1.35-3.96), but became statistically non-significant when adjusted for psychiatric comorbidity, and remained non-significant in further adjustments.

Alcohol use disorders also had a high rate of unnatural deaths (47.6%), and were associated with significantly increased mortality risk (adjusted HR 1.72, 95% CI 1.10-2.71).

Also depressive symptoms, measured with the BDI, were associated with increased mortality, without controlling for psychiatric disorders and controlling for other confounders (HR 1.53, 95% CI 1.11–2.11 for BDI score 10–18 and HR 1.77, 95%CI 1.09–2.86 for BDI score 19 or more).

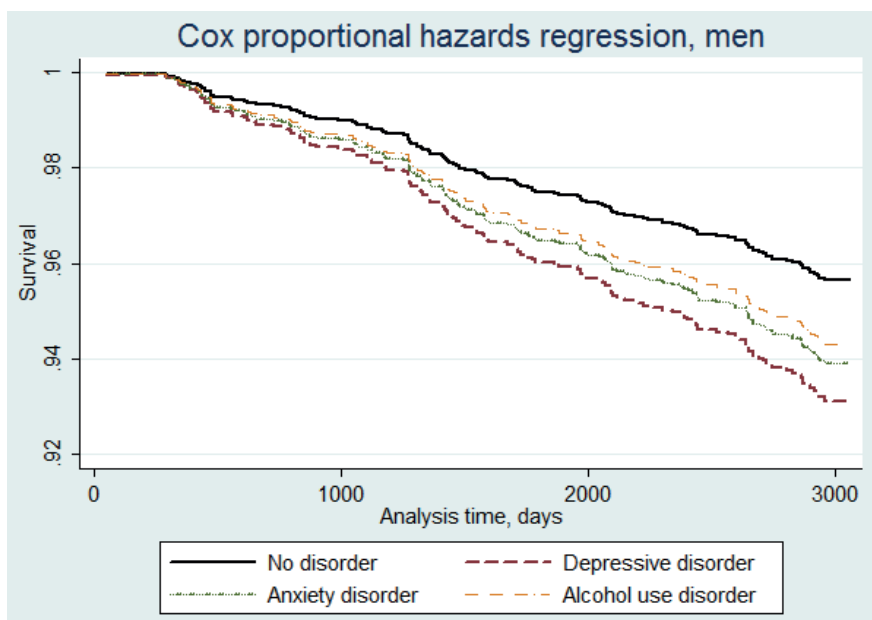
Figures 4-5 present survival curves for men and women with depressive, anxiety and alcohol use disorders, and without these disorders, adjusted for other risk factors (age, education, income, marital status, smoking status, BMI and somatic diseases (Markkula et al., previously unpublished results).



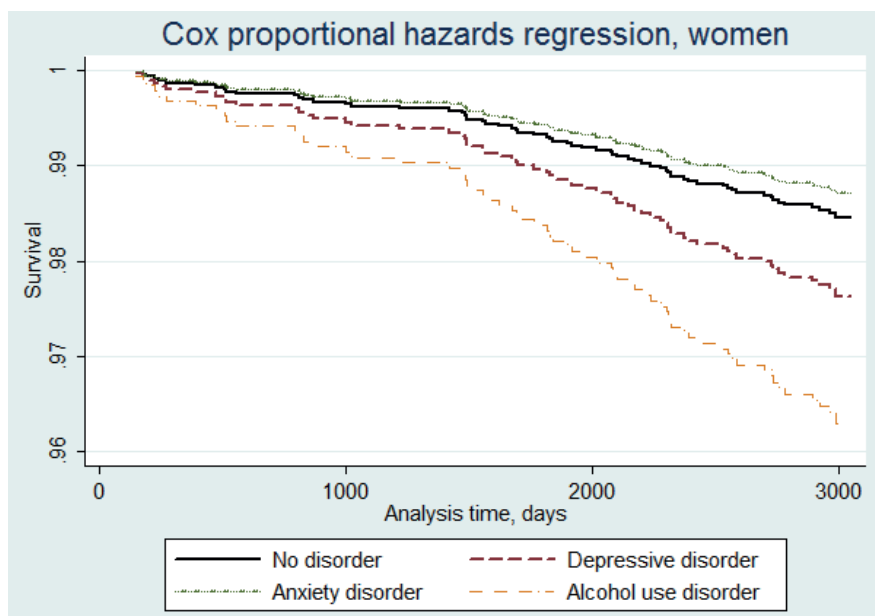
**Table 14.** *Mortality risk by psychiatric disorder and gender in unadjusted and adjusted models after 8-year follow-up (results by gender previously unpublished)*

	Unadjusted <sup>a</sup>		Adjusted for socioeconomic factors, health status and smoking <sup>a</sup>	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Any depressive disorder	2.40 (1.52-3.78)	<0.001	1.97 (1.15-3.39)	0.01
Men	2.78 (1.56-4.98)	0.001	1.84 (0.89-3.81)	0.099
Women	1.95 (0.97-3.94)	0.062	2.13 (0.92-4.92)	0.078
Any anxiety disorder	2.32 (1.35-3.96)	0.002	1.20 (0.58-2.45)	0.62
Men	2.82 (1.50-5.30)	0.001	1.39 (0.60-3.18)	0.441
Women	1.46 (0.50-4.26)	0.490	0.83 (0.21-3.29)	0.791
Any alcohol use disorder	2.55 (1.65-3.93)	<0.001	1.72 (1.10-2.71)	0.02
Men	2.40 (1.52-3.76)	0.000	1.52 (0.94-2.46)	0.088
Women	5.43 (1.42-20.6)	0.013	3.48 (0.68-17.7)	0.133

a. All models are stratified for age and sex. The adjusted model is also stratified for lifetime psychosis and history of cancer, and adjusted for education (low/intermediate/high), income quintile, marital status (married or cohabiting/other), smoking status (smoker/ex-smoker/never-smoker), BMI (<25/25-30/ >30), and somatic diseases (pulmonary, cardiovascular, musculoskeletal, vision and hearing, neurological, diabetes and other (psoriasis, inflammatory bowel disease, urinary incontinence, disturbing allergy)).



**Figure 4** Survival curves of men with depressive, anxiety and alcohol use disorders



**Figure 5** Survival curves of women with depressive, anxiety and alcohol use disorders

## **6 DISCUSSION**

### **6.1 SUMMARY OF THE MAIN RESULTS**

This longitudinal population study of depressive disorders examined prevalence, predictors and different adverse outcomes of depressive disorders in a general population setting. Specifically, the aims were to establish the prevalence of depressive disorders (major depressive disorder and dysthymia) in the Finnish population in 2011, and to assess possible changes in prevalence since 2000; to examine risk factors for new-onset depressive disorders; to investigate the long-term prognosis of depressive disorders in the population and different predictors of adverse outcomes; and to assess excess mortality in depressive, anxiety and alcohol use disorders.

The 12-month prevalence of depressive disorders in the Finnish general population aged 30 years and over was 9.6% (95% CI 7.9-11.3) in 2011. There was a significant increase in the prevalence from 2000 to 2011. Accounting for non-participation by multiple imputation increased the prevalence estimate by approximately two percentage points.

Risk factors for new-onset cases of depressive disorders were younger age, female gender, childhood adversities, lower trust axis of social capital, and having an anxiety disorder or subclinical depressive symptoms at baseline. In addition, having somatic diseases was a risk factor for dysthymia.

Of the persons with MDD at baseline, 34% still had some depressive, anxiety or alcohol use disorder after eleven years, and 48% had clinically significant depressive symptoms. Among those with dysthymia at baseline, the prognosis was worse: 43% had some depressive, anxiety or alcohol use disorder, and 61% had depressive symptoms at follow-up. Both groups also had worse health-related quality of life and self-rated health, indicating greater health needs. The difference to the general population was particularly noticeable among persons with baseline dysthymia. Unmarried persons and those with a more severe initial disorder had a higher risk of persistent course.

Persons with depressive disorders had a twofold mortality risk, whereas the risk was 1.7-fold in alcohol use disorders and not increased in anxiety disorders, when adjusted for age, sex, socioeconomic status, physical health and health behaviours. The mortality risk was higher among depressed men and in those with a more severe disorder.

## 6.2 POTENTIAL RISK FACTORS AND PREDICTORS OF NEGATIVE OUTCOMES OF DEPRESSION

### 6.2.1 GENDER AND AGE

In this study, women had a higher prevalence of MDD but not dysthymia, and their adjusted odds for current (prevalent) MDD, but not dysthymia, were increased. The risk for new-onset MDD was 1.5-fold in women. Prognosis of depressive disorders did not differ by gender except for the fact that depressed men had a higher mortality risk than women. In the separate mortality analyses, however, the hazard ratios were of similar magnitude in both genders, suggesting that the excess mortality in depressed men reflected the gender gap in life expectancy in the general population.

These findings are largely consistent with previous literature. Most studies have found women to have higher incidence of depression, approximately 1.5 to 2-fold (De Graaf *et al.*, 2002, Eaton *et al.*, 2008c, Klein *et al.*, 2013, Stegenga *et al.*, 2013, Wang *et al.*, 2010a). However, incidence of depression decreases in both genders after 30 years of age, and in the studied age group of 41-77 years, the gender difference is smaller than in young adulthood (Patten *et al.*, 2016, Pedersen *et al.*, 2014). Therefore, it is understandable that the risk difference was slightly smaller than in many studies examining younger populations.

Both the World Mental Health Surveys and a US national population survey found a higher prevalence of dysthymia in women (Blanco *et al.*, 2010, Seedat *et al.*, 2009). This differs from our finding, but there are few other studies to compare with. According to a meta-analysis, the mortality risk in depression is twofold in depressed men compared with depressed women. Also, as compared with the general population, depressed men have a higher mortality risk (RR 2.0) than women (RR 1.6) (Cuijpers *et al.*, 2014b). The higher mortality risk of men was observed in sub-study III (depressed men vs. depressed women) but not sub-study IV (depressed men and women vs. general population).

Why is the prevalence of MDD higher in women than in men? The question can be approached by examining which factors influence the magnitude of the risk difference. The risk difference between men and women peaks at 20 years; after 40 years, it is very small (Pedersen *et al.*, 2014). Women's higher risk thus appears to be related to different life stressors in adolescence and early adulthood. It has been suggested that the difference in early adolescence is related to: the differing ages at which boys and girls develop emotional maturity; the differences in the way boys and girls are brought up; and differing reactions to maternal depression and other negative life events

(Jenkins and Curwen, 2008, Zahn-Waxler *et al.*, 2000). Biological differences also influence the risk of depression and other mental disorders in later life through epigenetic mechanisms (Kigar and Auger, 2013). Hormonal changes in a woman's life, such as entering puberty, premenstrual symptoms, perinatal depression and menopause, might also explain part of the higher prevalence (Buttner *et al.*, 2013, Schiller *et al.*, 2015, Toffol *et al.*, 2015). Estrogens have been suggested to increase the risk of depression via two pathways – interactions with neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF), and their influence on the serotonergic system (Borrow and Cameron, 2014). Early menarche, for example, has been associated with increased risk of depressive symptoms in early adolescence (Joinson *et al.*, 2013). On the other hand, longer duration of the reproductive period may protect against postmenopausal depression (Georgakis *et al.*, 2016).

As previously noted, risk factors for depression differ between genders, with personality and interpersonal factors being more important among women, and externalising psychopathology, history of depression and stressful events related to financial and occupational problems more important among men (Kendler and Gardner, 2014). In early adulthood, women report more life events prior to the onset of depression, but this difference disappears later in life (Harkness *et al.*, 2010). It has been suggested that acute stressors increase the risk of MDD in women and substance use disorders in men, but the evidence to support this is mixed, and most likely the pathways are more complex than previously thought (Slopen *et al.*, 2011).

Between countries, the risk difference is higher in high-income countries (Rai *et al.*, 2013). On the other hand, Seedat *et al.* (Seedat *et al.*, 2009) found that the male-female difference decreased over time and was smaller where gender roles were more equal. They hypothesize that the increase in female employment opportunities and birth control has promoted women's mental health and reduced exposure to stressors.

Some of the higher prevalence of depression among women may be due to ways that depressive symptoms are conceptualised. For example, crying and loss of sexual desire are more frequent among women (Salokangas *et al.*, 2002). Consistent with this idea of different diagnostic thresholds, men who receive a diagnosis of a depressive disorder report more disability (Scott and Collings, 2010). The diagnostic criteria of depressive disorders, however, do not include these contentious symptoms, and it is unlikely that measurement bias would explain all of the gender difference in depression.

The prevalence and incidence of depressive disorders decreased with age, with the exception of prevalence of dysthymia, which remained stable. This is understandable, given the long-term course of the disorder, and in line with

earlier literature (Eaton *et al.*, 2008c, Kessler and Bromet, 2013, Stegenga *et al.*, 2013, Wang *et al.*, 2010a). Some of the decrease may be due to methodological issues: O'Connor and colleagues have shown that the rate of positive responses to the rather complicated CIDI screening questions shows a much steeper decline with age than responses to the simpler symptom-related items of the interview or symptom scales (O'Connor and Parslow, 2009, O'Connor and Parslow, 2010). Another consideration is the lower participation rate in the mental health interview by older individuals. Consistent with this, the prevalence rates in older age groups were influenced by multiple imputation more than the younger ones, and, at the same time, point estimates were less precise.

Nonwithstanding the limitations of psychometric instruments, it is possible that the impact of stressors in different stages in life influences the incidence of depressive disorders. Also, some personality features that predispose to depression may become subtler with increasing age, such as issues with interpersonal relationships and self-image. When comparing variation of depressive symptoms over the life course, both mild and severe depressive symptoms are less frequent in older age groups relative to younger ones, whereas symptoms classified as “despondent” (or deeply hopeless) did not decrease with age (Mezuk and Kendler, 2012).

### **6.2.2 SOCIOECONOMIC POSITION**

In this study, neither income nor education as measures of socioeconomic position (SEP) was associated with prevalence, incidence or outcomes of depressive disorders. The only exception was dysthymia, which was more prevalent among people with low education. A meta-analysis found a 1.8-fold prevalence and 1.2-fold incidence of depression among those with lowest SEP (Lorant *et al.*, 2003), but many individual studies from high-income countries have found no association. It is possible that the lack of association in incidence in our study is explained by thorough controlling for confounders, such as physical diseases and childhood adversities. In our study population, educational attainment was strongly correlated with age, as the educational level of the Finnish population has risen significantly over the past decades (Statistics Finland, 2015). This may also partly explain our lack of significant associations with education, since depressive disorders were more common among the younger age groups.

These results do not support the theory of direct causation from adult SEP to depression. On the other hand, childhood adversities, some directly and some indirectly linked to socioeconomic position, were a strong risk factor for depression. Similarly, in a study of Finnish adolescents, parental

socioeconomic position was strongly correlated with current depressive symptoms (Torikka *et al.*, 2014).

In another analysis of the working-age participants of the Health 2000 Survey, low income, but not education or manual occupation, was associated with a 1.7-fold odds of current depressive disorders, when adjusted for age, gender and marital status (Pulkki-Råbäck *et al.*, 2012). This finding, together with the fact that dysthymia was more prevalent among people with less education, could be interpreted to support the theory of selection: that depressive disorders cause downward movement on the socioeconomic scale, or prevent moving upwards. On the other hand, there could be common factors leading to both low SEP and depressive disorders. Finally, we did not specifically assess the impact of financial hardship, which has been a stronger predictor than objective measures of SEP (Skapinakis *et al.*, 2006, Wang *et al.*, 2010b, Weich and Lewis, 1998).

### 6.2.3 CHILDHOOD ADVERSITIES AND FAMILY HISTORY

In this study, an accumulation of three or more childhood adversities predicted onset of depressive disorders, particularly dysthymia. People with three or more childhood adversities also had a 1.9-fold risk for persistence of depressive disorder, but this association reduced and became non-significant after controlling for other confounding factors. Parental mental disorder was not associated with onset of depressive symptoms, but we were not able to examine the impact of parental depressive disorder specifically. Also, the information was based on self-report and only two questions, one on each parent's mental health, and therefore is not as reliable as prospective studies with standardised psychiatric evaluations of the parents. In earlier studies, parental mental disorder has been a risk factor for depression (Eaton *et al.*, 2001, Klein *et al.*, 2013, Stegenga *et al.*, 2013). However, in one study, the impact was mediated through childhood maltreatment (Plant *et al.*, 2015).

The impact of childhood adversity on the risk of depression is well-known in the literature (Bowes *et al.*, 2015, Park *et al.*, 2013, Pirkola *et al.*, 2005a, Ritsher *et al.*, 2001, Sourander *et al.*, 2015, Stegenga *et al.*, 2013) (Elovainio *et al.*, 2015), even though there is controversy over the reporting bias introduced by current depressive symptoms (Colman *et al.*, 2015). In this study, this was not a problem, as in Sub-study II, the individuals did not have depression at baseline, when childhood adversities were inquired. However, there may have been memory bias, as the study participants were middle-aged or older at the time of the interview.

In two studies examining the link between childhood adversities and chronic depressive disorder or psychological distress, the association was mediated

through personality pathology, such as avoidant or generally maladaptive personality (Klein *et al.*, 2015, Spinhoven *et al.*). In another study, the negative impact of childhood maltreatment on the course of depression was mediated by personality characteristics (Hovens *et al.*, 2016). This could explain how the risk remains increased in midlife and even later. Furthermore, according to the interpersonal theory of depression, negative interpersonal events in childhood, such as exposure to bullying, represent a type of trauma which may lead to development of depression similarly to other traumatic events in life (Sourander *et al.*, 2015). The cognitive theory suggests that peer victimisation, particularly verbal or relational, contributes to the development of negative self-cognitions, which predisposes a person to depression (Cole *et al.*, 2014).

It is worthwhile to note that we did not have information on childhood abuse, which has been found to be a particularly strong risk factor for depression. A meta-analysis of consequences of different types of abuse found the strongest influence on risk of depression in emotional abuse, followed by neglect and physical abuse (Norman *et al.*, 2012). Our results show that an accumulation of other forms of adversity, perhaps considered more benign in nature, does considerably increase the risk of depression. It may be encouraging news to families who face adversities that according to our study, it was the accumulation of three or more adversities that significantly increased the risk of depressive disorders.

#### **6.2.4 MARITAL STATUS AND SOCIAL CAPITAL**

In this study, single marital status (i.e. being never married, divorced, separated or widowed) was associated with a higher prevalence, but not a higher incidence, of depression, in addition to an increased risk of persistence of the disorder. It seems that single people do not have a higher risk of developing depression, but that the higher prevalence is instead due to reduced chance of recovery. Depressed individuals may also have a higher likelihood of ending a relationship or not starting one, but this was not examined in this study. Other studies have shown that mental disorders reduce the chances of marrying and increase the risk of divorce (Breslau *et al.*, 2011).

The higher prevalence of depression among single people is in line with earlier literature (Kessler and Bromet, 2013), and some studies have also found higher incidence (Anthony and Petronis, 1991, Scott *et al.*, 2010). Similar to our findings, other studies have found longer episode duration and a higher risk of recurrence among the unmarried (Eaton *et al.*, 2008c, van Loo *et al.*, 2015a). The association between marriage and depression also depends on customs and culture related to marriage: a study of married



Pakistani women showed that depression was associated with teenage and arranged marriage, and to different forms of abuse by the husband and his family (Ali *et al.*, 2009).

The increased risk of persistence of depression among the unmarried could be related to the detrimental effect of loneliness. Social isolation or loneliness is associated with depressive symptoms and to other negative health outcomes (Hawkley and Cacioppo, 2010). Also, social support is reduced among those who are not in a relationship (Joutsenniemi *et al.*, 2006). It seems that having a partner is of particular importance to mental health, beyond the role of increased social capital that a relationship entails.

We found that social capital, and specifically its trust axis, was protective against new-onset depressive disorders. Among people with baseline depression, low participation and low trust were associated with having more depressive symptoms at follow-up in the weighted-only analyses.

The questions measuring trust dealt with feeling safe in the neighbourhood; cynical mistrust; and feeling disappointed or surprised by the behaviour of people close to you. The construct of “trust” as a component of social capital is closely related to personality features and the way an individual interprets the neighbourhood and the people surrounding them. The features that allow an individual to express trust in relation to their surroundings could also make them more resilient to the life stressors that increase the risk of depression. Interestingly, one study found no association between social capital and incidence of depression, when controlling for personality features (Noteboom *et al.*, 2015). In addition to personal characteristics, however, the concept of cynical mistrust also reflects the surrounding social environment (Nieminen *et al.*, 2008), and an environment of little trust between people could thus predispose to depression. Another longitudinal study has also shown that both cynical hostility and cynical mistrust were strong risk factors for later depressive symptoms (Nabi *et al.*, 2010b).

Low participation showed an association with new-onset depression that disappeared when confounders were controlled for. Of note is the lack of association between support and both incidence and persistence of depression. This highlights the importance of individual characteristics and actions over passively received support.

## 6.2.5 CHRONIC SOMATIC CONDITIONS

We found a higher incidence of dysthymia among persons with chronic somatic conditions at baseline. Somatic comorbidity was not associated with persistence with depressive disorders.

Having one or two chronic diseases increased the risk of new-onset dysthymia, but not MDD. In other studies, chronic physical diseases have been associated with incidence of depression (Kaplan *et al.*, 1987, Patten, 2001, Stegenga *et al.*, 2013, Wang *et al.*, 2010a) and longer course of illness (Patten, 2005, Patten *et al.*, 2010). The Canadian NPHS, which is the largest study to document association between chronic physical diseases and depression, used an instrument that does not differentiate between types of depression, and therefore it is not possible to assess whether it was the risk of MDD or dysthymia that was increased.

The mechanism by which chronic physical diseases increase the risk of dysthymia could be a common underlying factor or causal pathway such as inflammation (Kiecolt-Glaser *et al.*, 2015). Or it could be related to the experience of living with a chronic illness and its consequences, such as loss of the ability to work or the loss of functional capacity. Finally, detection of depression among people with chronic somatic conditions may be particularly challenging (Menear *et al.*, 2015), and it is possible that undetected depressive symptoms become chronic in this population. Most likely, the higher risk of depression in this population is a combination of these and other factors.

#### **6.2.6 OTHER PSYCHIATRIC DISORDERS AND PSYCHOLOGICAL SYMPTOMS**

We found significantly higher incidence of MDD among people with anxiety disorders. Psychiatric comorbidity was not associated with persistence of depressive disorders, although this has been commonly found in other studies (Kessler *et al.*, 2008, Rhebergen *et al.*, 2011). Baseline depressive symptoms were predictive of later onset of depressive disorders among people with no depression at baseline. Among people with baseline depression, severity of depressive symptoms was a strong predictor of all negative outcomes: persistence of disorder, level of depressive symptoms at follow-up and mortality.

Similar to our findings, previous studies have found higher incidence of MDD among people with anxiety disorders (Eaton *et al.*, 2008c, Kessler *et al.*, 2008, Klein *et al.*, 2013, Stegenga *et al.*, 2013). Developmentally, the genetic etiology in anxiety and depressive symptoms seems to be independent in childhood, but shared from adolescence onwards, with an overarching internalising genetic factor (Waszczuk *et al.*, 2014). In addition to common genetic risk factors, there can be other common underlying risk factors, such as childhood adversity, personality features, negative life experiences, or the direct impact of the anxiety disorder as a stressor, as well

as its consequences, such as social isolation (Kessler *et al.*, 2008, Moreno-Peral *et al.*, 2014, Moscati *et al.*, 2015). Remarkably, alcohol use disorders did not increase the risk of depressive disorders in this study. A meta-analysis found a twofold risk of MDD among people with alcohol use disorder (Boden and Fergusson, 2011).

The fact that subclinical depressive symptoms predicted later onset of depression is to be expected, and is frequently found in other studies (Ernst *et al.*, 1992, Horwath *et al.*, 1992, Klein *et al.*, 2013, Skapinakis *et al.*, 2006). These could have been an indicator of a depressive episode about to begin already close to baseline, or they may reflect a way of expressing emotions, or a personality trait.

It is intuitive that the severity of the disorder also predicted persistence, and this is line with previous findings (Lamers *et al.*, 2016, Penninx *et al.*, 2011). However, it is notable that depressed people with more depressive symptoms at baseline also had higher mortality. This may reflect a particular subtype of depression with higher mortality risk (Ziegelstein, 2015), or simply that the mechanisms leading to excess mortality in depression are more pronounced in more severe disorders. A previous study found increased mortality risk already present in persons with mild depressive symptoms, and an increase in mortality risk with more severe symptoms (White *et al.*, 2015).

### **6.3 INCREASING PREVALENCE OF DEPRESSIVE DISORDERS AND IMPACT OF NON-PARTICIPATION**

The annual prevalence of depressive disorders in the Finnish population increased from 7.3% in 2000 to 9.6% in 2011. The increase was more notable in women than men, and in MDD than in dysthymia. Unfortunately, no direct explanation for the increase can be derived from this study. However, based on the established risk factors for depression, some speculations can be made. In 2000, Finland was experiencing steady economic growth, whereas in 2011, there was an economic recession. Economic crisis is associated with negative mental health impacts such as depression and increase in suicide rates (Stuckler *et al.*, 2009, Wahlbeck and McDaid, 2012). The impact is mediated via increased unemployment and poverty, individual financial difficulties, alcohol-related harm, social exclusion and family strain (Wahlbeck and McDaid, 2012). It is possible that the economic downturn contributed to the increase in prevalence of depressive disorders in Finland.

Considering that childhood adversities predict onset of depressive disorders, some explanation to increasing rates of depression can also be found in the previous recession of the early 1990s, when many families experienced

unemployment and financial difficulties as well as other adverse consequences, such as parental alcohol use. In 2011, people who lived their childhood during the recession of the early 1990s were in their early 30s, and thus part of the Health 2011 sample. There is abundant evidence of the psychological malaise of the generation born in 1987 (Paananen *et al.*, 2013a, Paananen *et al.*, 2013b), and it is likely that the negative impact of the 1990s recession extends beyond this cohort.

In keeping with our finding of increasing prevalence, during the same observation period, 2001-2011, the prevalence of self-reported depression increased among all adolescents, and doubled among adolescents whose parents were unemployed (Torikka *et al.*, 2014). This further highlights the role of family social adversity as a contributor to the increasing prevalence of depression.

We found significantly higher prevalence rates of depressive disorders when accounting for non-participation by multiple imputation than by inverse probability weights only. Based on this, it is evident that non-participation of people with mental disorders in health surveys introduces a downward bias in all population survey based prevalence estimates that do not correct for non-participation (Haapea *et al.*, 2008). This should be taken into account when analysing and comparing studies on prevalence of mental disorders. Based on our results, multiple imputation seems to be a more effective way of correcting for non-participation than the more traditional weighting.

## **6.4 MORTALITY IN DEPRESSIVE, ANXIETY AND ALCOHOL USE DISORDERS**

We found excess mortality in all studied categories of mental disorders: unadjusted, the hazard ratio was 2.4 for depressive; 2.3 for anxiety; and 2.6 for alcohol use disorders. When adjusted, however, the risk was twofold in depressive disorders, and 1.7-fold in alcohol use disorders, but no longer significant (HR 1.2) in anxiety disorders. Both anxiety and alcohol use disorders had a high rate of unnatural deaths. Among depressed people, older individuals, men, and people with more depressive symptoms had higher mortality.

Our results regarding excess mortality in depressive disorders are in line with recent reviews and meta-analyses that found 1.5 to 1.9-fold mortality risks (Baxter *et al.*, 2011, Cuijpers *et al.*, 2014a, Ferrari *et al.*, 2013a, Walker *et al.*, 2015). The mortality risk was increased despite extensive controlling for confounders and long follow-up, factors that had been associated with smaller risk in previous studies, and in a general population sample as opposed to a clinical one, which also have higher mortality rates (Cuijpers *et*

*al.*, 2014a). Of note, our sample included only people with unipolar depression. Most other studies and none of the recent four reviews mention explicitly whether only unipolar depression was considered. It seems, however, that this would not significantly impact the results, as mortality in bipolar disorder is similar to depressive disorders (Walker *et al.*, 2015; Hayes *et al.*, 2015).

Based on our results, the approximately twofold risk reported by the meta-analyses does not appear to be exaggerated or inflated by low-quality studies. This supports the saying that there truly is no health without mental health (Prince *et al.*, 2007).

A recent meta-analysis found a higher mortality risk among depressed men (HR 2.0) than among women (HR 1.6) (Cuijpers *et al.*, 2014b). We had similar results in Sub-study III, where depressed men had a higher mortality risk than did women. However, in Sub-study IV, there was little difference in mortality risk between men and women in the magnitude of the risk. The only exception was alcohol use disorders, where the risk was 1.5-fold for men and 3.5-fold for women, although due to the small number of observations, neither was statistically significant.

Unfortunately, there was not enough data to draw conclusions on the excess mortality in specific disorders, and thus the mortality risk in dysthymia remains unknown.

Mortality risk in anxiety disorders (HR 1.2) was smaller in magnitude than reported in a recent meta-analysis (HR 1.4) (Walker *et al.*, 2015) and not significant. Separated by gender, the risk was larger in men than in women, as in an earlier study in the Netherlands (van Hout *et al.*, 2004), but not significant in either sex. The mortality risk became non-significant when controlled for comorbid depressive and alcohol use disorders. It is possible that not all studies examining mortality in anxiety disorders have been able to control for comorbid depressive disorders, which may have biased the results.

Excess mortality in alcohol use disorders was similar to that found in earlier studies (Eaton *et al.*, 2008a, Harris and Barraclough, 1998), and similar to the twofold risk found in a meta-analysis of general population studies (Roerecke and Rehm, 2013), but lower than the 3.5-fold risk in the most recent meta-analysis (Laramée *et al.*, 2015). However, most of the studies in the meta-analysis simply compared age and gender-controlled mortality rates without further adjustments. The fact that we controlled carefully for many physical, mental and behavioural risk factors might explain our lower risk estimate. Also, mortality was lower in studies where cases were selected from the general population and not from treatment centres, and those with

longer follow-up, both findings in line with our lower risk estimate. The mortality risk was higher in women than in men, which is also consistent with earlier studies (John *et al.*, 2013, Roerecke and Rehm, 2013).

## **6.5 METHODOLOGICAL CONSIDERATIONS – STRENGTHS AND LIMITATIONS**

### **6.5.1 POPULATION SURVEY DATA**

This was a longitudinal population-based study, which has several benefits over other study settings. First, as opposed to studies based on clinical samples or treatment-based registers, a population-based study includes both subjects who have sought treatment and those who have not. Therefore, conclusions regarding depressive disorders can be made without the bias related to differing help-seeking behaviours (Susukida *et al.*, 2015). Second, unlike cross-sectional studies, we were able to draw conclusions on temporal associations between potential risk factors and depressive disorders, and also describe outcomes of the disorders. Third, as this was a general health survey, we had extensive information on the subjects' physical health status.

However, the longitudinal population setting also posed some limitations. Even though the study sample was large, the number of people diagnosed with depression at baseline or follow-up was not sufficient to carry out many analyses by subgroups, such as gender, age group or type of depression. Likewise, when analysing many potential risk factors simultaneously, the statistical power was reduced, resulting in widening confidence intervals.

The fact that the survey covered a broad range of health indicators limited the time available for questions regarding mental health. As a result, we did not have information on, for example, lifetime disorders, and therefore could not exclude certain conditions, such as bipolar disorder at follow-up. Also, we did not have information on the participants' mental health between the baseline and follow-up interview, which could have been acquired using a more detailed mental health interview or more detailed register data. The question regarding childhood adversities could have been influenced by recall bias. Due to the limited time available for both the mental health interview and mental health instruments, we did not include instruments to measure personality features, which are important risk factors of depression. Finally, we were not able to analyse specific symptoms or clusters of symptoms, and whether they had specific risk factors, which has been found in other studies (Fried *et al.*, 2014).

### 6.5.2 THE CIDI INTERVIEW

The Composite International Diagnostic Interview, Munich version (M-CIDI) (Wittchen and Pfister, 1997) was used to diagnose depressive, anxiety and alcohol use disorders in the study. It is one of the most widely used structured interviews in population surveys worldwide, including the WHO World Mental Health Survey (Kessler and Ustun, 2004), and provides excellent opportunities for cross-country comparison. The Munich version of the CIDI has good test-retest reliability (Wittchen *et al.*, 1998), and, when compared with clinician diagnoses in a treatment setting, has excellent sensitivity and specificity (95-100 and 93-100, respectively) (Reed *et al.*, 1998).

However, in a community sample, where disorders are less common than in a clinical setting, the CIDI performs only moderately well. Two studies have compared CIDI to the SCID, which is the gold standard of psychometric instruments: the NCS-R and the WMHS. In these studies, the CIDI managed to capture only 55-69% of persons with depression (sensitivity), and 95-97% of the persons without depression (specificity). In the studied populations, this led to rather low precision (positive predictive value), 50-55% (Haro *et al.*, 2006, Kessler *et al.*, 2003).

Nevertheless, at the population-level, the CIDI neither inflates nor deflates the annual prevalence of mental disorders, when compared with the SCID (Haro *et al.*, 2006). Therefore, our prevalence estimate can be considered an accurate estimate of the prevalence of depressive disorders, as defined in the diagnostic manuals. However, it is possible that some subjects identified as “cases” of depressive disorders by the CIDI in this study would not have been identified as such by a more detailed or semi-structured interview. The opposite is also true: the CIDI may have missed some cases. It is difficult to assess what, if any, impact this would have had on our results on risk factors and prognosis.

### 6.5.3 NON-PARTICIPATION AND MULTIPLE IMPUTATION

Selective non-participation complicated the analyses in Sub-studies I-III. Previous studies have shown that psychiatric disorders are associated with non-participation (de Graaf *et al.*, 2000, Eaton *et al.*, 1992, Haapea *et al.*, 2008, Suvisaari *et al.*, 2009). Therefore, the fact that the participation rate in the mental health interview was only 57%, poses a challenge to the analysis and interpretation of the results.

The method chosen to account for non-participation was multiple imputation (MI), which is considered superior to other methods of handling missing

data (Li *et al.*, 2015, Mackinnon, 2010). Register data, which was available for all participants, was used in the imputation. The variables included in the imputation model were chosen based on their correlation with both missingness and with the outcomes, depressive disorders. Sensitivity analyses were carried out with varying numbers of imputed data sets. The results based on MI are thus considered more reliable and are reported as primary results. In the case of Sub-studies II-III, there was little difference between the weighted-only and imputed results. In Sub-study I, however, the prevalence was very different, which is understandable given the increased non-participation among people with hospitalisations for depression or other mental disorders. For this reason, the results cannot be considered as reliable as results based on a sample with a higher participation rate. Also, there was considerable imprecision in the point estimates based on results where imputation had a larger impact, such as prevalence among the older age groups.

Finally, the register data used in the imputation only included people with hospitalisations for mental disorders, and was not able to capture people in outpatient treatment, or those without treatment. Also, lifetime instead of past year treatments were utilised in the imputation. It is difficult to assess the impact of these limitations of the register data on the imputed results. However, the fact that any register data was available for imputation can be considered an advantage over other, less complete sources of information for imputation.



## 7 CONCLUSIONS

This study contributed to the existing body of literature documenting the large burden of depressive disorders. It showed that depressive disorders are common in the Finnish population and that their prevalence has increased over the past decade; that certain negative experiences and individual characteristics place people at a higher risk of developing these disorders; that depressive disorders often have a chronic course and negative consequences on the individual's life and health; and that people with depressive and alcohol use disorders have a higher mortality risk than the general population.

The findings of this study are in line with earlier literature and bring clarity to some issues where controversial findings existed. The impact of non-participation on prevalence estimates should be taken into account in health surveys, and also in estimates of burden of mental disorders. Unlike previous studies from earlier decades, we found an increasing prevalence of depressive disorders. Further studies should examine whether this is a global phenomenon or specific to Finland.

In terms of reducing the burden of depressive disorders, it is crucial to focus efforts on prevention. Several types of psychological interventions, both targeted and universal, are effective in preventing incidence of depression (van Zoonen *et al.*, 2014). Based on this study, people with subclinical depressive symptoms, anxiety disorders, low trust and multiple childhood adversities are at a particularly high risk of developing depression and could be suitable target groups for preventive interventions. In addition, welfare policies should target families with children to minimise the impact of parental illness, unemployment, financial difficulties and other adversities on children (Wahlbeck and McDaid, 2012). Specific policies to reduce bullying could be effective in reducing incidence of depression (Scott *et al.*, 2014).

We found no evidence of low socioeconomic position being a risk factor for depression, but dysthymia was more prevalent among those with low or intermediate education. There was no evidence to support the causation theory, where low socioeconomic position causes depression. Since dysthymia was more prevalent among those with low education, and previously low income has been associated with current depressive disorders in the same survey, selection seems more likely than causation to explain the link between depressive disorders and low SEP in the Finnish context. Therefore, policy efforts should aim at protecting persons with persistent depression from downward social mobility or failure to achieve desired educational and income level. These efforts could include reduction of stigma

and discrimination in educational institutions and work places, and improving early access to treatment (Muntaner *et al.*, 2004). Stigma related to depression is still very common, with 41% of people with MDD in high-income countries reporting being “shunned” or avoided by others, and 23% reporting discrimination in regard to their physical health problems (Lasalvia *et al.*, 2015).

As opposed to new-onset depression, we found few predictors of persistence of depression. However, in clinical treatment settings, it is important to recognise that severity of the disorder is an important predictor of the longitudinal course, perhaps more so than comorbidity or other individual characteristics. The fact that unmarried people are more likely to have a persistent course of illness means that they warrant special attention in treatment settings. Research efforts could be directed toward finding better ways to distinguish those at a higher risk of adverse outcomes. Recently, a more densely connected network of symptoms was found to predict longitudinal course of depression in a network analysis using Bayesian methods (van Borkulo *et al.*, 2015). Different prediction algorithms have been developed to predict risk of recurrence in depressed people (van Loo *et al.*, 2015a, Wang *et al.*, 2014), where a wide variety of risk factors, including demographic characteristics, level of depressive and anxiety symptoms, psychiatric and family history, physical health and life events, contribute to the risk of recurrence.

Beyond the diagnostic status and remission, we found broad and long-term adverse outcomes in subclinical symptoms, health-related quality of life and self-rated health. All of these were more pronounced in individuals with dysthymia, even after recovery from the disorder was achieved. Since the negative health impacts of depressive disorders persist more than a decade after the initial diagnosis, a history of depressive disorder should be regarded as a sign of increased health needs in the health care system, and a system of periodical general health check-ups could be considered even after formal recovery. Also self-care and monitoring in the recovery period could be encouraged, and different online and other tools developed for this purpose.

As did numerous other studies, we found increased mortality among people with depressive and alcohol use disorders, and the risk was increased despite long follow-up and extensive controlling for confounders. Little doubt remains over the excess mortality in mental disorders. In fact, as Graham Thornicroft writes: “It has been clear for more than 50 years that people with the more disabling forms of mental illness do not live as long as those without mental illness. -- What are the implications of these sobering findings? Three things are clear. Firstly, the time for descriptive research alone is over. We now need evidence-based interventions that can reduce excess mortality. -- Thirdly, this huge loss of life among people with mental

illness needs to be recognised as a human rights disgrace.” (Thornicroft, 2013) In the same spirit, Suetani comments: “Scarce research money would be better invested in assessing how to implement proven interventions and in developing better treatments and prevention strategies.” (Suetani *et al.*, 2015). These interventions to reduce excess mortality include adequate treatment of depression, both antidepressants and psychological treatment (Cuijpers and Schoevers, 2004). The physical health needs of persons with mental disorders and the inequities in access to health care also need to be adequately addressed (Lawrence and Kisely, 2010).

Based on this study, recommendations for further research include:

1. Assess recent trends of prevalence of depressive disorders in other settings besides Finland;
2. Identify reasons for the increasing prevalence of depressive disorders, particularly in women;
3. Examine ways to improve participation of people with mental disorders in population studies and the statistical methods to account for their non-participation;
4. Identify better predictors of different negative outcomes of depressive disorders that can be used in the clinical practice;
5. Assess implementation and effectiveness of interventions to reduce excess mortality in mental disorders.

Some policy recommendations based on this study are:

1. Target preventive programmes to people with subclinical depressive symptoms, anxiety disorders, low trust, and childhood adversities;
2. Sustain implementation of welfare policies that target families with children to minimise the impact of parental illness, unemployment, financial difficulties and other adversities, in order to prevent onset of depressive disorders in these children. Implement policies to reduce bullying and assess their impact on reducing incidence of depression;
3. Protect individuals with depression from downward social movement, or failure to achieve desired educational level, via reduction of stigma and discrimination in educational institutions and work places, facilitating return to work after sick leave, and improving early access to treatment;
4. Offer special support to unmarried or lonely depressed individuals, either at the treatment facilities or the non-governmental sector;
5. Implement policies to tackle the vast inequity in mortality between people with mental disorders and those without. Address the physical health needs of people with mental disorders, both during the symptomatic phase and after formal recovery.

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Variability of Gingival Crevicular Fluid Matrix Metalloproteinase -8 Levels in Respect to Point-of-Care Diagnostics in Periodontal Diseases

